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References
1. Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH. Hyponatremia treatment guidelines 2007: expert panel recommendations. Am J Med. 2007;120(11 Suppl 1):S1-S21.
2. Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, Orlandi C. for the SALT Investigators. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for Hyponatremia. N Engl J Med 2006;355:2099-112

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Aims and Scope

Electrolytes & Blood Pressure (EBP; ISSN 1738-5997), formerly known as the Korean Journal of Electrolyte Metabolism, is the official journal of the Korean Society for Electrolyte and Blood Pressure Research (formerly the Korean Society of Electrolyte Metabolism). Since its launch in 2003, the journal has evolved into a respected and internationally recognized publication. As of 2005, it has been published exclusively in English as a peer-reviewed platform dedicated to advancing scientific knowledge in its field. The journal is indexed under the ISO abbreviation Electrolyte Blood Press.

The primary aim of *Electrolytes & Blood Pressure* is to serve as a distinguished forum for the publication and dissemination of high-quality research and comprehensive review articles that deepen our understanding of the complex physiological and pathological processes underlying renal function and blood pressure regulation. The journal welcomes contributions across a wide range of disciplines, with particular emphasis on the mechanisms and clinical relevance of solute and water transport, acidification, urine concentration, vasoactive mediators, nephrolithiasis, inherited kidney disorders, and aging-related changes in renal physiology. A distinctive focus of the journal lies in translational research—investigations that effectively bridge basic laboratory discoveries with their clinical applications in the diagnosis, treatment, and management of disorders involving fluid and electrolyte balance, acid-base homeostasis, and renal hypertension. By promoting the integration of molecular, physiological, and clinical approaches, the journal seeks to foster interdisciplinary dialogue and innovation in nephrology and cardiovascular research.

Journal Infomation

The journal is currently indexed in several major international databases, including Scopus, PubMed, PubMed Central (PMC), KoreaMed, KoMCI, EMBASE, Chemical Abstracts Service (CAS), Google Scholar, and Korea Citation Index (KCI), ensuring its accessibility and discoverability within the global scientific community.

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Review Article

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From Ion Channels to Blood Pressure: Genetic Disorders of Renal Tubular Transport

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ABSTRACT

Blood pressure regulation is fundamentally dependent on renal sodium and electrolyte handling. Genetic disorders of renal tubular transport provide representative evidences that illuminate the molecular mechanisms linking ion channels to systemic hemodynamics. Monogenic conditions such as Bartter syndrome, Gitelman syndrome, Liddle syndrome, and Gordon syndrome demonstrate how specific alterations in tubular sodium, potassium, chloride, and magnesium transport translate into distinct blood pressure phenotypes. Salt-wasting disorders are characterized by hypokalemic metabolic alkalosis and low or normal blood pressure despite activation of the renin–angiotensin–aldosterone system, underscoring the dominant role of tubular sodium loss. In contrast, gain-of-function mutations enhancing distal sodium reabsorption produce volume expansion, suppressed renin levels, and hypertension, often accompanied by characteristic electrolyte abnormalities. These conditions highlight the tight coupling between sodium and potassium handling and reveal how small perturbations in distal nephron transport can exert disproportionate effects on blood pressure. Insights from these rare genetic syndromes extend beyond monogenic disease. Variants in genes regulating Na^+-Cl^- cotransporter, epithelial sodium channel, and with-no-lysine signaling pathways contribute to salt sensitivity and low-renin hypertension in the general population. Understanding tubular channelopathies thus provides a mechanistic framework for precision diagnosis and targeted therapy in hypertension. The current review examines how renal ion channel dysfunction translates from molecular defects to systemic blood pressure regulation.

Keywords: Blood pressure; Ion channels; Kidney tubules; Mutation; Water-electrolyte balance

INTRODUCTION

Blood pressure homeostasis is inseparably linked to renal sodium and electrolyte handling. Since kidney plays the central role in long-term blood pressure control [1-3], it has become evident that sustained hypertension cannot occur without an accompanying disturbance in renal sodium balance. The kidney determines extracellular fluid volume through tightly regulated tubular reabsorption of sodium, chloride, potassium, and other electrolytes [4,5].

Even subtle alterations in transporters can produce significant and sustained changes in systemic hemodynamics [6].

In the proximal tubule, the majority of filtered sodium is reabsorbed through coordinated activity of exchangers and cotransporters [7,8]. The thick ascending limb (TAL) establishes the corticomedullary gradient via Na-K-2Cl cotransporter (NKCC2)-mediated sodium chloride transport [9], while the distal convoluted tubule (DCT) and collecting duct perform critical "fine-tuning" of sodium reabsorption under hormonal control [10,11]. Among these, the distal nephron is particularly influential in determining final sodium excretion and potassium balance [12]. Because only a small fraction of filtered sodium reaches these segments, modest changes in transporter activity can disproportionately affect extracellular volume and blood pressure [13].

Genetic disorders of renal tubular transport provide compelling evidence that illuminate the molecular basis of blood pressure regulation [14-16]. Rare monogenic conditions affecting specific ion channels or regulatory pathways may result in electrolyte imbalances accompanied by distinct blood pressure phenotypes [17,18]. For example, loss-of-function mutations in transporters of the TAL or DCT lead to renal salt wasting, hypokalemic metabolic alkalosis, activation of the renin–angiotensin–aldosterone system (RAAS), and paradoxically low or normal blood pressure [19,20]. In contrast, gain-of-function mutations enhancing distal sodium reabsorption produce volume expansion, suppressed renin levels, and hypertension, often with characteristic potassium disturbances [21-23]. These genetic disturbances demonstrate that tubular sodium handling can override systemic hormonal signals in determining arterial pressure (**Fig. 1**).

Beyond rare Mendelian disorders, accumulating evidence suggests that common genetic variants in these same pathways contribute to interindividual differences in salt sensitivity and susceptibility to essential hypertension [24-26]. Polymorphisms affecting epithelial sodium channel (ENaC) subunits, with-no-lysine (WNK) kinases, and related regulatory proteins have been associated with blood pressure variation across populations [27,28]. Therefore, the molecular mechanisms uncovered through the study of monogenic tubular disorders extend to the broader landscape of polygenic hypertension.

In this review, we will examine how genetic disorders of renal tubular transport elucidate the mechanistic link between ion channels and systemic blood pressure regulation. By integrating segment-specific physiology, characteristic electrolyte patterns, and clinical phenotypes, this review will provide a cohesive framework that connects molecular defects to hemodynamic outcomes. Understanding these channelopathies not only enhances diagnostic insight into rare disorders but also offers broader implications for the pathogenesis and treatment of hypertension.

TUBULAR ELECTROLYTE HANDLING AND BLOOD PRESSURE

Proximal tubule

The proximal tubule reabsorbs approximately 60–70% of filtered sodium and water, making it a major determinant of extracellular fluid volume and systemic blood pressure [1,7]. Sodium reabsorption in this segment is primarily mediated by the apical Na^+/H^+ exchanger

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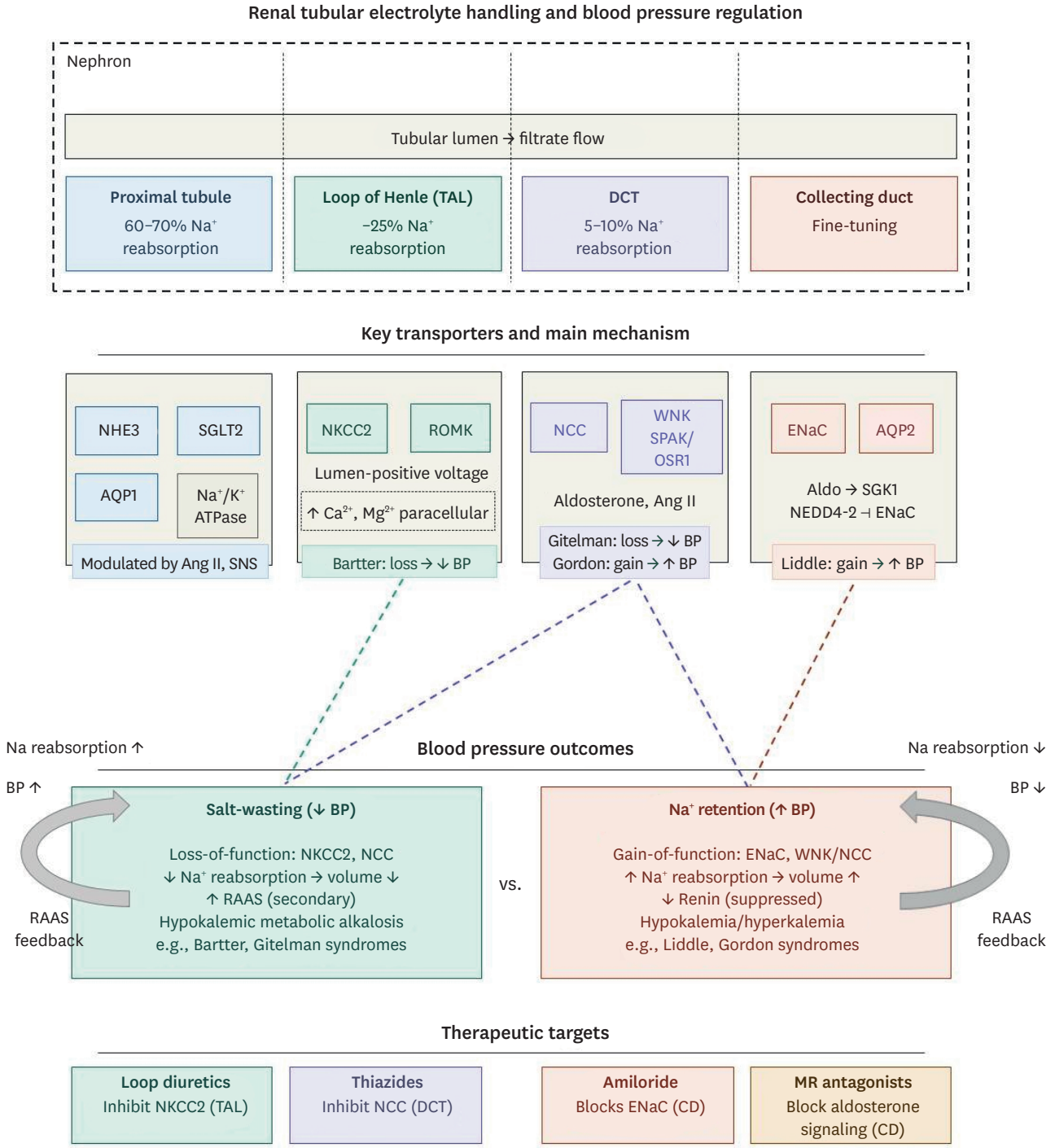

Fig. 1. Renal tubular electrolyte handling and its impact on BP regulation. Schematic overview of electrolyte transport along the nephron and its contribution to BP regulation. The proximal tubule reabsorbs approximately 60–70% of filtered Na^+, followed by 25% reabsorption in the TAL, 5–10% in the DCT, and fine-tuning in the CD. Key transporters include NHE3, SGLT2, AQP1, and Na^+/K^+-ATPase in the proximal tubule; NKCC2 and ROMK in the TAL, which generate a lumen-positive voltage driving paracellular Ca^{2+} and Mg^{2+} reabsorption; NCC in the DCT; and ENaC and AQP2 in the CD, which are regulated by aldosterone and vasopressin, respectively. WNK-SPAK/OSR1 signaling modulates NCC activity in the DCT. Differential regulation of these transporters results in distinct BP outcomes. Enhanced NKCC2, NCC, or ENaC activity leads to Na^+ retention and volume expansion, contributing to hypertension, as seen in conditions such as Liddle syndrome, Gordon syndrome, and hyperaldosteronism. Conversely, loss-of-function or inhibition of NKCC2, NCC, or ENaC promotes natriuresis and salt-wasting, associated with hypotension and disorders such as Bartter and Gitelman syndromes. Therapeutic interventions targeting these pathways include loop diuretics (NKCC2 inhibitors), thiazide diuretics (NCC inhibitors), ENaC blockers (e.g., amiloride), and mineralocorticoid receptor antagonists that inhibit aldosterone signaling. AQP1, aquaporin-1; AQP2, aquaporin-2; BP, blood pressure; CD, collecting duct; DCT, distal convoluted tubule; ENaC, epithelial sodium channel; NCC, Na^+-Cl^- cotransporter; NHE3, Na^+/H^+ exchanger; NKCC2, Na-K-2Cl cotransporter; OSR1, oxidative stress-responsive kinase 1; RAAS, renin–angiotensin–aldosterone system; ROMK, renal outer medullary potassium; SGLT, sodium-glucose cotransporters; SNS, sympathetic nervous system; SPAK, Ste20-related proline-alanine-rich kinase; TAL, thick ascending limb; WNK, with-no-lysine.

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(NHE3), sodium-glucose cotransporters (SGLT1 and SGLT2), and various sodium–solute cotransport systems [7,8]. SGLT1 is primarily located in the intestinal epithelium and contribute to glucose absorption in the gut while SGLT2 is primarily located in kidney proximal tubule (S1 and S2 segments) and contribute up to 97% of glucose reabsorption in the proximal tubule. SGLT1 in the proximal tubule S2/S3 segments only reabsorb ~3% of glucose in the proximal tubule. Chloride and bicarbonate handling are tightly coupled to sodium transport, and osmotic water reabsorption occurs through aquaporin-1 channels [7,11]. Importantly, proximal tubular sodium transport is modulated by angiotensin II and sympathetic nervous system activity, both of which enhance NHE3 activity and promote volume expansion [6,8]. Genetic or acquired dysregulation of proximal sodium transport alters pressure-natriuresis relationships, thereby contributing to hypertension or, conversely, salt-wasting states [1,3,6].

Loop of Henle

The TAL of the loop of Henle reabsorbs approximately 25% of filtered sodium via the apical NKCC2, functioning as a key site for urinary concentration and medullary gradient formation [1,9]. Potassium recycling through renal outer medullary potassium (ROMK) channels generates a lumen-positive transepithelial voltage that drives paracellular reabsorption of calcium and magnesium [29,30]. Because the TAL is impermeable to water, solute reabsorption without water contributes to dilution of tubular fluid and maintenance of the corticomedullary osmotic gradient [31]. Mutations affecting NKCC2, ROMK, or associated regulatory proteins disrupt sodium reabsorption and typically result in salt wasting and hypotension, as observed in Bartter syndromes [18]. Conversely, enhanced TAL sodium transport increases extracellular volume and elevates blood pressure [3,6]. This segment also participates in tubule-glomerular feedback via macula densa by sensing luminal NaCl and linking tubular electrolyte handling to glomerular hemodynamics and systemic pressure regulation [32,33].

DCT

The DCT reabsorbs approximately 5–10% of filtered sodium, primarily through the thiazide-sensitive Na^+-Cl^- cotransporter (NCC) [10]. Although quantitatively smaller than proximal segments, sodium handling in the DCT exerts disproportionate effects on blood pressure because it lies downstream of the macula densa and is tightly regulated by hormonal and kinase signaling pathways [6,10]. The WNK and its downstream target kinases (Ste20-related proline-alanine-rich kinase [SPAK] and oxidative stress-responsive kinase 1 [OSR1]) play a central role in modulating NCC activity in response to intracellular chloride concentration and hormonal stimuli such as aldosterone and angiotensin II [34]. Gain-of-function mutations in WNK kinases or NCC cause enhanced sodium reabsorption and hypertension, as seen in pseudo-hypoaldosteronism type II (Gordon syndrome), whereas loss-of-function mutations result in Gitelman syndrome with hypotension and hypokalemia [21,22]. Therefore, the DCT represents a critical fine-tuning segment linking electrolyte transport to long-term blood pressure control [6,10].

Collecting duct

The collecting duct is the final regulatory site for sodium, potassium, and water balance, integrating systemic hormonal signals to determine net sodium retention [11,12]. Principal cells mediate sodium reabsorption via ENaC, with basolateral Na^+/K^+-ATPase maintaining the electrochemical gradient. ENaC activity is strongly regulated by aldosterone and modulated by serum- and glucocorticoid-regulated kinase 1 and the E3 ubiquitin ligase neural precursor

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cell expressed, developmentally down-regulated 4-2 (NEDD4-2) [13]. Water permeability in this segment is controlled by vasopressin-dependent insertion of aquaporin-2 channels, linking osmotic regulation to blood pressure [35,36]. Gain-of-function mutations in ENaC result in Liddle syndrome characterized by hypertension and suppressed renin–aldosterone levels, whereas loss-of-function mutations lead to salt-wasting hypotension [13,23]. Through its hormone-sensitive and pressure-responsive properties, the collecting duct serves as a final checkpoint translating electrolyte handling into sustained changes in extracellular volume and arterial pressure [6].

MONOGENIC DISORDERS AFFECTING BLOOD PRESSURE

Bartter syndrome

Bartter syndrome comprises a group of autosomal recessive disorders caused by loss-of-function mutations affecting ion transporters in the TAL of the loop of Henle [14,20]. The most common genetic defects involve *SLC12A1* encoding NKCC2 (type I), *KCNJ1* encoding ROMK (type II), *CLCNKB* encoding ClC-Kb (type III), and *BSND* encoding barttin (type IV) (**Table 1**) [18,37]. These mutations impair NKCC2 or associated potassium recycling and chloride exit across the basolateral membrane [9]. Functionally, reduced NKCC2 activity abolishes lumen-positive transepithelial voltage, leading to diminished paracellular calcium and magnesium reabsorption [38]. The resulting defect in sodium chloride reabsorption produces renal salt wasting, volume contraction, and secondary activation of the RAAS. Despite marked hyperreninemia and hyperaldosteronism, patients typically exhibit normal or low blood pressure due to persistent renal sodium loss [6,37,39]. Clinically, Bartter syndrome is characterized by hypokalemic metabolic alkalosis, hypercalciuria, polyuria, and growth retardation, with antenatal forms presenting as polyhydramnios and premature birth [17,20,37].

Gitelman syndrome

Gitelman syndrome is an autosomal recessive disorder caused by loss-of-function mutations in *SLC12A3*, which encodes the thiazide-sensitive NCC in the DCT (**Table 1**) [17]. Inactivation of NCC reduces sodium and chloride reabsorption in this segment, increasing distal sodium delivery to the collecting duct [10]. Enhanced sodium reabsorption through ENaC in principal cells promotes potassium and hydrogen ion secretion, resulting in hypokalemic metabolic alkalosis. Unlike Bartter syndrome, impaired NCC activity also enhances proximal calcium reabsorption and reduces magnesium uptake in the DCT, leading to hypocalciuria and hypomagnesemia [19,20]. The chronic renal salt wasting induces mild extracellular

Table 1. Monogenic renal tubular disorders: electrolyte abnormalities, blood pressure, and underlying transport defects

Disorder	Affected nephron segment	Subtype	Key transporter (subtype)	Gene	Electrolyte abnormalities	Acid–base status	Blood pressure	Clinical features
Bartter syndrome	Thick ascending limb	I II III IV	NKCC2 ROMK ClC-Kb Barttin	*SLC12A1* *KCNJ1* *CLCNKB* *BSND*	↓ K^+, ↑ Ca^{2+} (hypercalciuria) ± ↓ Mg^{2+}	Metabolic alkalosis	Low/normal	Polyuria, polydipsia, growth retardation, antenatal polyhydramnios
Gitelman syndrome	Distal convoluted tubule		NCC	*SLC12A3*	↓ K^+, ↓ Mg^{2+}, ↓ Ca^{2+} (hypocalciuria)	Metabolic alkalosis	Low/normal	Muscle cramps, fatigue, tetany, chondrocalcinosis
Liddle syndrome	Collecting duct		ENaC	*SCNN1A*, *SCNN1B*, *SCNN1G*	↓ K^+	Metabolic alkalosis	High	Early-onset hypertension, low renin, low aldosterone
Gordon syndrome (PHAII)	Distal convoluted tubule		NCC	*WNK1*, *WNK4*, *KLHL3*, *CUL3*	↑ K^+, normal Ca^{2+}	Metabolic acidosis	High	Hyperkalemia, salt-sensitive hypertension, thiazide-responsive

ENaC, epithelial sodium channel; NCC, Na^+-Cl^- cotransporter; NKCC2, Na-K-2Cl cotransporter; ROMK, renal outer medullary potassium.

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volume contraction and compensatory RAAS activation, yet systemic blood pressure is typically low or normal [18,19]. Clinically, patients present with muscle weakness, cramps, fatigue, tetany, and sometimes chondrocalcinosis in adulthood [40]. The phenotype resembles chronic thiazide diuretic exposure, reflecting the central role of NCC in blood pressure regulation [10,17].

Liddle syndrome

Liddle syndrome is an autosomal dominant form of hypertension caused by gain-of-function mutations in genes encoding subunits of the ENaC, including *SCNN1A*, *SCNN1B*, and *SCNN1G* (**Table 1**) [23,41,42]. Most mutations disrupt the proline-rich PY motif in the β or γ subunit, preventing binding of the ubiquitin ligase NEDD4-2 and thereby impairing ENaC degradation [23,42]. The resulting increase in apical ENaC surface expression enhances sodium reabsorption in principal cells of the collecting duct independent of aldosterone [43]. Increased sodium retention expands extracellular volume and suppresses renin and aldosterone levels, distinguishing Liddle syndrome from other hyperaldosteronism states [23]. Enhanced electrogenic sodium uptake also increases potassium and hydrogen ion secretion, leading to hypokalemic metabolic alkalosis [12]. Clinically, patients develop early-onset hypertension, often severe, with suppressed plasma renin activity and low aldosterone concentrations [42]. The disorder responds to ENaC inhibitors such as amiloride rather than mineralocorticoid receptor antagonists, highlighting its aldosterone-independent mechanism [16,42].

Gordon syndrome (pseudo-hypoaldosteronism type 2)

Gordon syndrome is an autosomal dominant hypertensive disorder characterized by hyperkalemia and metabolic acidosis, resulting from increased sodium chloride reabsorption in the DCT [21]. Causative mutations involve components of the WNK signaling pathway, including *WNK1*, *WNK4*, *KLHL3*, and *CUL3* (**Table 1**) [21,22]. These mutations enhance activation of the WNK–SPAK/OSR1 kinase cascade, leading to increased phosphorylation and activity of NCC [21]. Enhanced NCC-mediated sodium reabsorption reduces distal sodium delivery to the collecting duct, thereby decreasing potassium and hydrogen ion secretion. The net effect is extracellular volume expansion, suppression of renin, and hypertension accompanied by hyperkalemia [44-46]. Unlike Liddle syndrome, aldosterone levels are often normal or mildly elevated but insufficient to overcome the potassium retention caused by reduced distal sodium delivery. Clinically, patients present with familial hypertension, hyperkalemia, and sensitivity to thiazide diuretics, which directly inhibit NCC and correct both blood pressure and electrolyte abnormalities.

GENETIC POLYMORPHISMS IN ION CHANNELS AFFECTING BLOOD PRESSURE

Beyond rare monogenic disorders, common genetic polymorphisms in renal ion channels and their regulatory pathways contribute to interindividual variability in blood pressure within the general population [24-26]. Genome-wide association studies have identified variants in genes encoding sodium transporters and associated signaling molecules—including *SLC12A3* (NCC), *SCNN1A*/*SCNN1G* (ENaC subunits), *WNK1*, and components of the RAAS pathway—that are associated with modest but measurable differences in systolic and diastolic blood pressure [24,26,47]. Unlike pathogenic mutations that markedly disrupt transporter function, these polymorphisms typically induce subtle alterations in channel

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expression, trafficking, or phosphorylation state, thereby slightly shifting tubular sodium reabsorption efficiency. Even small changes in cumulative sodium handling can alter the pressure–natriuresis relationship over time, influencing salt sensitivity and long-term cardiovascular risk [47,48]. Importantly, environmental factors such as dietary sodium intake interact with these genetic variants, highlighting the polygenic and multifactorial nature of essential hypertension. Understanding how common ion channel polymorphisms modulate renal sodium transport may improve risk stratification and enable more personalized antihypertensive strategies.

THERAPEUTIC IMPLICATIONS

Many widely used diuretics target the same transporters implicated in monogenic blood pressure disorders, demonstrating the translational relevance of renal tubular physiology [49]. Loop diuretics inhibit NKCC2 in the TAL, thiazide diuretics target NCC in the DCT, and potassium-sparing agents such as amiloride directly block ENaC in the collecting duct. The clinical phenotypes of Bartter, Gitelman, Liddle, and Gordon syndromes mirror the pharmacologic effects of these agents, providing mechanistic insight into drug responsiveness [50]. For example, patients with Liddle syndrome respond to ENaC inhibition rather than mineralocorticoid receptor antagonists, whereas individuals with Gordon syndrome demonstrate marked sensitivity to thiazide therapy due to NCC hyperactivity.

Beyond rare monogenic conditions, interindividual variability in transporter activity may influence treatment response in essential hypertension [50,51]. Genetic polymorphisms affecting NCC, ENaC, WNK signaling, or RAAS components may partially explain differences in salt sensitivity and diuretic efficacy [50-52]. This raises the possibility of genotype-guided antihypertensive therapy, in which patients with enhanced distal sodium reabsorption preferentially benefit from thiazide or ENaC inhibition, while those with predominant volume expansion may respond more favorably to loop diuretics or RAAS blockade. Furthermore, emerging therapies targeting aldosterone synthase, mineralocorticoid receptor signaling, or novel regulators of the WNK–SPAK pathway may offer more selective modulation of renal sodium handling [53,54].

Taken together, advances in understanding renal ion channel genetics and physiology support a shift toward precision medicine in hypertension, where therapeutic selection is informed not only by blood pressure level but also by the underlying mechanisms of sodium retention and volume regulation [6,26,50].

CONCLUSION

Renal tubular electrolyte handling constitutes the central determinant of blood pressure regulation. Segment-specific sodium transport—from bulk reabsorption in the proximal tubule to fine-tuning in the distal nephron and collecting duct—collectively shapes extracellular volume, pressure–natriuresis dynamics, and systemic arterial pressure. Monogenic disorders such as Bartter, Gitelman, Liddle, and Gordon syndromes provide important evidences demonstrating how discrete alterations in ion channels or their regulatory pathways can shift sodium balance and profoundly influence blood pressure phenotype.

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Beyond rare genetic diseases, common polymorphisms affecting ion transporters and associated signaling networks contribute to interindividual variability in salt sensitivity and hypertension risk. These findings reinforce the concept that essential hypertension is, at least in part, a disorder of renal sodium handling modulated by polygenic and environmental interactions. Importantly, many current antihypertensive therapies directly target the same transport systems implicated in these genetic conditions, highlighting the translational bridge between renal physiology and clinical practice.

Future advances in genomic profiling and phenotyping may enable more precise classification of hypertensive patients based on underlying tubular transport abnormalities. A thorough understanding of ion channel regulation, intracellular signaling pathways, and gene–environment interactions will be essential for the development of personalized therapeutic strategies. Ultimately, integrating renal physiology, genetics, and clinical medicine offers a path toward mechanism-based management of blood pressure and improved cardiovascular outcomes.

REFERENCES

1. Guyton AC. Blood pressure control—special role of the kidneys and body fluids. *Science* 1991;252:1813-1816. PUBMED | CROSSREF
2. Guyton AC, Coleman TG, Cowley AV Jr, Scheel KW, Manning RD Jr, Norman RA Jr. Arterial pressure regulation. Overriding dominance of the kidneys in long-term regulation and in hypertension. *Am J Med* 1972;52:584-594. PUBMED | CROSSREF
3. Cowley AW Jr, Roman RJ. The role of the kidney in hypertension. *JAMA* 1996;275:1581-1589. PUBMED | CROSSREF
4. Hamlyn JM, Blaustein MP. Sodium chloride, extracellular fluid volume, and blood pressure regulation. *Am J Physiol* 1986;251:F563-F575. PUBMED | CROSSREF
5. Danziger J, Hoenig MP. The role of the kidney in disorders of volume: core curriculum 2016. *Am J Kidney Dis* 2016;68:808-816. PUBMED | CROSSREF
6. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. *Cell* 2001;104:545-556. PUBMED | CROSSREF
7. Curthoys NP, Moe OW. Proximal tubule function and response to acidosis. *Clin J Am Soc Nephrol* 2014;9:1627-1638. PUBMED | CROSSREF
8. McDonough AA. Mechanisms of proximal tubule sodium transport regulation that link extracellular fluid volume and blood pressure. *Am J Physiol Regul Integr Comp Physiol* 2010;298:R851-R861. PUBMED | CROSSREF
9. Castrop H, Schießl IM. Physiology and pathophysiology of the renal Na-K-2Cl cotransporter (NKCC2). *Am J Physiol Renal Physiol* 2014;307:F991-F1002. PUBMED | CROSSREF
10. Subramanya AR, Ellison DH. Distal convoluted tubule. *Clin J Am Soc Nephrol* 2014;9:2147-2163. PUBMED | CROSSREF
11. Zeidel ML. Hormonal regulation of inner medullary collecting duct sodium transport. *Am J Physiol* 1993;265:F159-F173. PUBMED | CROSSREF
12. Stokes JB. Sodium and potassium transport by the collecting duct. *Kidney Int* 1990;38:679-686. PUBMED | CROSSREF
13. Schafer JA. Abnormal regulation of ENaC: syndromes of salt retention and salt wasting by the collecting duct. *Am J Physiol Renal Physiol* 2002;283:F221-F235. PUBMED | CROSSREF
14. Zelikovic I. Molecular pathophysiology of tubular transport disorders. *Pediatr Nephrol* 2001;16:919-935. PUBMED | CROSSREF
15. Hamilton KL, Butt AG. The molecular basis of renal tubular transport disorders. *Comp Biochem Physiol A Mol Integr Physiol* 2000;126:305-321. PUBMED | CROSSREF
16. Scheinman SJ, Guay-Woodford LM, Thakker RV, Warnock DG. Genetic disorders of renal electrolyte transport. *N Engl J Med* 1999;340:1177-1187. PUBMED | CROSSREF

17. Simon DB, Karet FE, Hamdan JM, Di Pietro A, Sanjad SA, Lifton RP. Bartter's syndrome, hypokalaemic alkalosis with hypercalciuria, is caused by mutations in the Na-K-2Cl cotransporter NKCC2. *Nat Genet* 1996;13:183-188. PUBMED | CROSSREF

18. Simon DB, Lifton RP. Ion transporter mutations in Gitelman's and Bartter's syndromes. *Curr Opin Nephrol Hypertens* 1998;7:43-47. PUBMED | CROSSREF

19. Knoers NV, Levtchenko EN. Gitelman syndrome. *Orphanet J Rare Dis* 2008;3:22. PUBMED | CROSSREF

20. Seyberth HW. An improved terminology and classification of Bartter-like syndromes. *Nat Clin Pract Nephrol* 2008;4:560-567. PUBMED | CROSSREF

21. Wilson FH, Disse-Nicodème S, Choate KA, et al. Human hypertension caused by mutations in WNK kinases. *Science* 2001;293:1107-1112. PUBMED | CROSSREF

22. Boyden LM, Choi M, Choate KA, et al. Mutations in kelch-like 3 and cullin 3 cause hypertension and electrolyte abnormalities. *Nature* 2012;482:98-102. PUBMED | CROSSREF

23. Yang KQ, Xiao Y, Tian T, Gao LG, Zhou XL. Molecular genetics of Liddle's syndrome. *Clin Chim Acta* 2014;436:202-206. PUBMED | CROSSREF

24. Ehret GB. Genome-wide association studies: contribution of genomics to understanding blood pressure and essential hypertension. *Curr Hypertens Rep* 2010;12:17-25. PUBMED | CROSSREF

25. Padmanabhan S, Caulfield M, Dominiczak AF. Genetic and molecular aspects of hypertension. *Circ Res* 2015;116:937-959. PUBMED | CROSSREF

26. Evangelou E, Warren HR, Mosen-Ansorena D, et al. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. *Nat Genet* 2018;50:1412-1425. PUBMED | CROSSREF

27. Gu X, Gu D, He J, et al. Resequencing epithelial sodium channel genes identifies rare variants associated with blood pressure salt-sensitivity: the GenSalt study. *Am J Hypertens* 2018;31:205-211. PUBMED | CROSSREF

28. Huan T, Esko T, Peters MJ, et al. A meta-analysis of gene expression signatures of blood pressure and hypertension. *PLoS Genet* 2015;11:e1005035. PUBMED | CROSSREF

29. Gamba G, Friedman PA. Thick ascending limb: the Na^+:K^+:$2Cl^-$ co-transporter, NKCC2, and the calcium-sensing receptor, CaSR. *Pflugers Arch* 2009;458:61-76. PUBMED | CROSSREF

30. Zacchia M, Capolongo G, Rinaldi L, Capasso G. The importance of the thick ascending limb of Henle's loop in renal physiology and pathophysiology. *Int J Nephrol Renovasc Dis* 2018;11:81-92. PUBMED | CROSSREF

31. Dantzler WH, Layton AT, Layton HE, Pannabecker TL. Urine-concentrating mechanism in the inner medulla: function of the thin limbs of the loops of Henle. *Clin J Am Soc Nephrol* 2014;9:1781-1789. PUBMED | CROSSREF

32. Schnermann J, Briggs JP. Tubuloglomerular feedback: mechanistic insights from gene-manipulated mice. *Kidney Int* 2008;74:418-426. PUBMED | CROSSREF

33. Edwards A, Castrop H, Laghmani K, Vallon V, Layton AT. Effects of NKCC2 isoform regulation on NaCl transport in thick ascending limb and macula densa: a modeling study. *Am J Physiol Renal Physiol* 2014;307:F137-F146. PUBMED | CROSSREF

34. Richardson C, Rafiqi FH, Karlsson HK, et al. Activation of the thiazide-sensitive Na^+-Cl^- cotransporter by the WNK-regulated kinases SPAK and OSR1. *J Cell Sci* 2008;121:675-684. PUBMED | CROSSREF

35. Wilson JL, Miranda CA, Knepper MA. Vasopressin and the regulation of aquaporin-2. *Clin Exp Nephrol* 2013;17:751-764. PUBMED | CROSSREF

36. Schrier RW. Vasopressin and aquaporin 2 in clinical disorders of water homeostasis. *Semin Nephrol* 2008;28:289-296. PUBMED | CROSSREF

37. Florea L, Caba L, Gorduza EV. Genetic heterogeneity in Bartter syndrome: clinical and practical importance. *Front Pediatr* 2022;10:908655. PUBMED | CROSSREF

38. Al Shibli A, Narchi H. Bartter and Gitelman syndromes: spectrum of clinical manifestations caused by different mutations. *World J Methodol* 2015;5:55-61. PUBMED | CROSSREF

39. Mrad FCC, Soares SBM, de Menezes Silva LAW, Dos Anjos Menezes PV, Simões-E-Silva AC. Bartter's syndrome: clinical findings, genetic causes and therapeutic approach. *World J Pediatr* 2021;17:31-39. PUBMED | CROSSREF

40. Cruz DN, Shaer AJ, Bia MJ, Lifton RP, Simon DB; Yale Gitelman's and Bartter's Syndrome Collaborative Study Group. Gitelman's syndrome revisited: an evaluation of symptoms and health-related quality of life. *Kidney Int* 2001;59:710-717. PUBMED | CROSSREF

41. Hansson JH, Nelson-Williams C, Suzuki H, et al. Hypertension caused by a truncated epithelial sodium channel γ subunit: genetic heterogeneity of Liddle syndrome. *Nat Genet* 1995;11:76-82. PUBMED | CROSSREF

42. Tetti M, Monticone S, Burrello J, et al. Liddle syndrome: review of the literature and description of a new case. *Int J Mol Sci* 2018;19:812. PUBMED | CROSSREF

43. Knight KK, Olson DR, Zhou R, Snyder PM. Liddle's syndrome mutations increase Na^+ transport through dual effects on epithelial Na^+ channel surface expression and proteolytic cleavage. *Proc Natl Acad Sci U S A* 2006;103:2805-2808. PUBMED | CROSSREF

44. Cornelius RJ, Maeoka Y, Shinde U, McCormick JA. Familial hyperkalemic hypertension. *Compr Physiol* 2024;14:5839-5874. PUBMED | CROSSREF

45. Rafael C, Hadchouel J. Familial Hyperkalemic Hypertension (FHHt). In: Caprio M, Fernandes-Rosa FL, eds. Hydro Saline Metabolism: Epidemiology, Genetics, Pathophysiology, Diagnosis and Treatment. Springer; 2023. p. 97-139.

46. Hadchouel J, Delaloy C, Fauré S, Achard JM, Jeunemaitre X. Familial hyperkalemic hypertension. *J Am Soc Nephrol* 2006;17:208-217. PUBMED | CROSSREF

47. An C, Yang L, Han T, et al. Kidney ion handling genes and their interaction in blood pressure control. *Biosci Rep* 2022;42:BSR20220977. PUBMED | CROSSREF

48. Ji W, Foo JN, O'Roak BJ, et al. Rare independent mutations in renal salt handling genes contribute to blood pressure variation. *Nat Genet* 2008;40:592-599. PUBMED | CROSSREF

49. Ellison DH. Clinical pharmacology in diuretic use. *Clin J Am Soc Nephrol* 2019;14:1248-1257. PUBMED | CROSSREF

50. Vormfelde SV, Burckhardt G, Zirk A, Wojnowski L, Brockmöller J. Pharmacogenomics of diuretic drugs: data on rare monogenic disorders and on polymorphisms and requirements for further research. *Pharmacogenomics* 2003;4:701-734. PUBMED | CROSSREF

51. Cooper-DeHoff RM, Johnson JA. Hypertension pharmacogenomics: in search of personalized treatment approaches. *Nat Rev Nephrol* 2016;12:110-122. PUBMED | CROSSREF

52. Vormfelde SV, Sehrt D, Toliat MR, et al. Genetic variation in the renal sodium transporters NKCC2, NCC, and ENaC in relation to the effects of loop diuretic drugs. *Clin Pharmacol Ther* 2007;82:300-309. PUBMED | CROSSREF

53. Ferdaus MZ, McCormick JA. The CUL3/KLHL3-WNK-SPAK/OSR1 pathway as a target for antihypertensive therapy. *Am J Physiol Renal Physiol* 2016;310:F1389-F1396. PUBMED | CROSSREF

54. Brown A, Meor Azlan NF, Wu Z, Zhang J. WNK-SPAK/OSR1-NCC kinase signaling pathway as a novel target for the treatment of salt-sensitive hypertension. *Acta Pharmacol Sin* 2021;42:508-517. PUBMED | CROSSREF

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Review Article

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From Ion Channels to Blood Pressure: Genetic Disorders of Renal Tubular Transport

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ABSTRACT

Blood pressure regulation is fundamentally dependent on renal sodium and electrolyte handling. Genetic disorders of renal tubular transport provide representative evidences that illuminate the molecular mechanisms linking ion channels to systemic hemodynamics. Monogenic conditions such as Bartter syndrome, Gitelman syndrome, Liddle syndrome, and Gordon syndrome demonstrate how specific alterations in tubular sodium, potassium, chloride, and magnesium transport translate into distinct blood pressure phenotypes. Salt-wasting disorders are characterized by hypokalemic metabolic alkalosis and low or normal blood pressure despite activation of the renin–angiotensin–aldosterone system, underscoring the dominant role of tubular sodium loss. In contrast, gain-of-function mutations enhancing distal sodium reabsorption produce volume expansion, suppressed renin levels, and hypertension, often accompanied by characteristic electrolyte abnormalities. These conditions highlight the tight coupling between sodium and potassium handling and reveal how small perturbations in distal nephron transport can exert disproportionate effects on blood pressure. Insights from these rare genetic syndromes extend beyond monogenic disease. Variants in genes regulating Na^+-Cl^- cotransporter, epithelial sodium channel, and with-no-lysine signaling pathways contribute to salt sensitivity and low-renin hypertension in the general population. Understanding tubular channelopathies thus provides a mechanistic framework for precision diagnosis and targeted therapy in hypertension. The current review examines how renal ion channel dysfunction translates from molecular defects to systemic blood pressure regulation.

Keywords: Blood pressure; Ion channels; Kidney tubules; Mutation; Water-electrolyte balance

INTRODUCTION

Blood pressure homeostasis is inseparably linked to renal sodium and electrolyte handling. Since kidney plays the central role in long-term blood pressure control [1-3], it has become evident that sustained hypertension cannot occur without an accompanying disturbance in renal sodium balance. The kidney determines extracellular fluid volume through tightly regulated tubular reabsorption of sodium, chloride, potassium, and other electrolytes [4,5].

Even subtle alterations in transporters can produce significant and sustained changes in systemic hemodynamics [6].

In the proximal tubule, the majority of filtered sodium is reabsorbed through coordinated activity of exchangers and cotransporters [7,8]. The thick ascending limb (TAL) establishes the corticomedullary gradient via Na-K-2Cl cotransporter (NKCC2)-mediated sodium chloride transport [9], while the distal convoluted tubule (DCT) and collecting duct perform critical "fine-tuning" of sodium reabsorption under hormonal control [10,11]. Among these, the distal nephron is particularly influential in determining final sodium excretion and potassium balance [12]. Because only a small fraction of filtered sodium reaches these segments, modest changes in transporter activity can disproportionately affect extracellular volume and blood pressure [13].

Genetic disorders of renal tubular transport provide compelling evidence that illuminate the molecular basis of blood pressure regulation [14-16]. Rare monogenic conditions affecting specific ion channels or regulatory pathways may result in electrolyte imbalances accompanied by distinct blood pressure phenotypes [17,18]. For example, loss-of-function mutations in transporters of the TAL or DCT lead to renal salt wasting, hypokalemic metabolic alkalosis, activation of the renin–angiotensin–aldosterone system (RAAS), and paradoxically low or normal blood pressure [19,20]. In contrast, gain-of-function mutations enhancing distal sodium reabsorption produce volume expansion, suppressed renin levels, and hypertension, often with characteristic potassium disturbances [21-23]. These genetic disturbances demonstrate that tubular sodium handling can override systemic hormonal signals in determining arterial pressure (**Fig. 1**).

Beyond rare Mendelian disorders, accumulating evidence suggests that common genetic variants in these same pathways contribute to interindividual differences in salt sensitivity and susceptibility to essential hypertension [24-26]. Polymorphisms affecting epithelial sodium channel (ENaC) subunits, with-no-lysine (WNK) kinases, and related regulatory proteins have been associated with blood pressure variation across populations [27,28]. Therefore, the molecular mechanisms uncovered through the study of monogenic tubular disorders extend to the broader landscape of polygenic hypertension.

In this review, we will examine how genetic disorders of renal tubular transport elucidate the mechanistic link between ion channels and systemic blood pressure regulation. By integrating segment-specific physiology, characteristic electrolyte patterns, and clinical phenotypes, this review will provide a cohesive framework that connects molecular defects to hemodynamic outcomes. Understanding these channelopathies not only enhances diagnostic insight into rare disorders but also offers broader implications for the pathogenesis and treatment of hypertension.

TUBULAR ELECTROLYTE HANDLING AND BLOOD PRESSURE

Proximal tubule

The proximal tubule reabsorbs approximately 60–70% of filtered sodium and water, making it a major determinant of extracellular fluid volume and systemic blood pressure [1,7]. Sodium reabsorption in this segment is primarily mediated by the apical Na^+/H^+ exchanger

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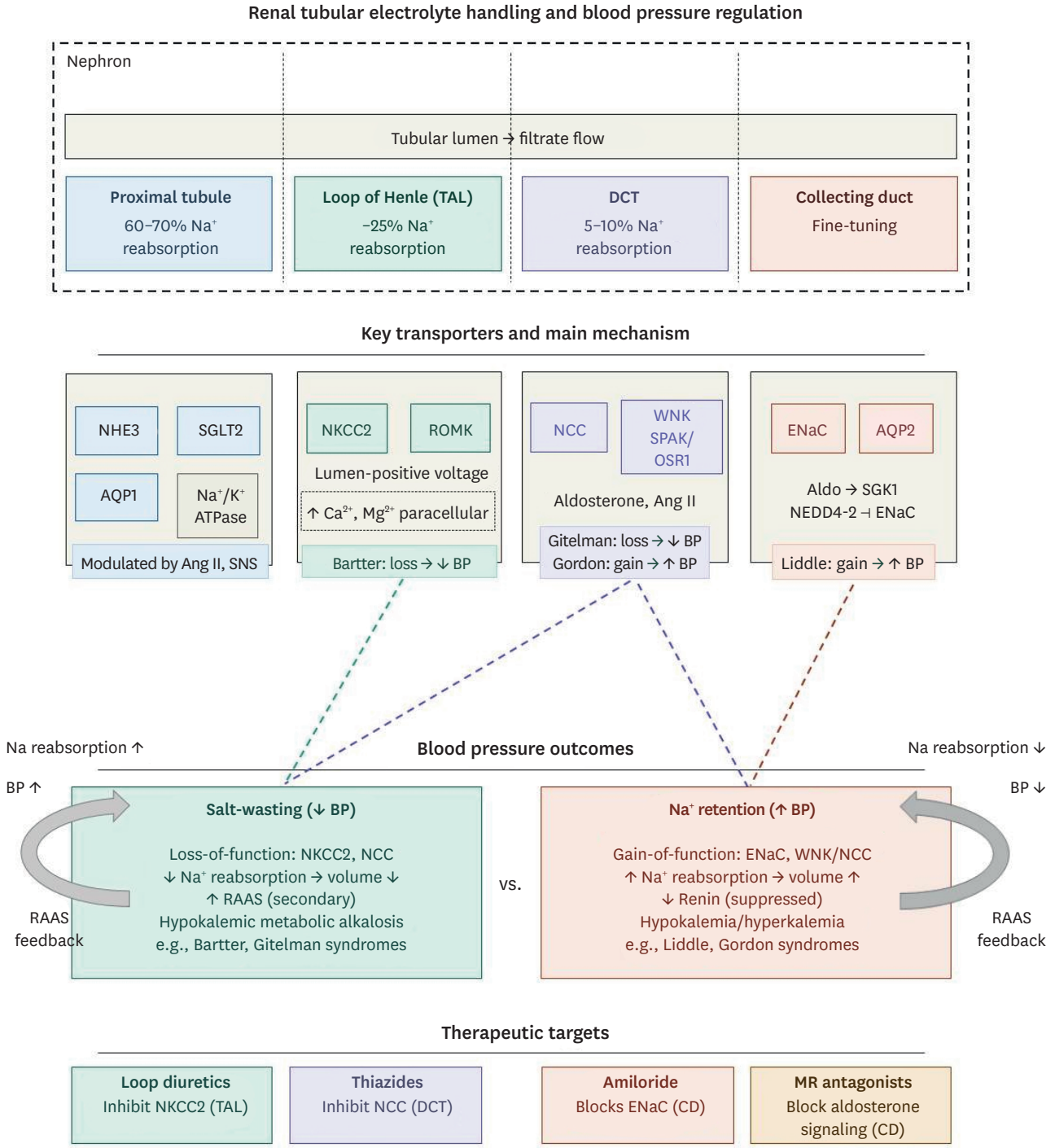

Fig. 1. Renal tubular electrolyte handling and its impact on BP regulation. Schematic overview of electrolyte transport along the nephron and its contribution to BP regulation. The proximal tubule reabsorbs approximately 60–70% of filtered Na^+, followed by 25% reabsorption in the TAL, 5–10% in the DCT, and fine-tuning in the CD. Key transporters include NHE3, SGLT2, AQP1, and Na^+/K^+-ATPase in the proximal tubule; NKCC2 and ROMK in the TAL, which generate a lumen-positive voltage driving paracellular Ca^{2+} and Mg^{2+} reabsorption; NCC in the DCT; and ENaC and AQP2 in the CD, which are regulated by aldosterone and vasopressin, respectively. WNK-SPAK/OSR1 signaling modulates NCC activity in the DCT. Differential regulation of these transporters results in distinct BP outcomes. Enhanced NKCC2, NCC, or ENaC activity leads to Na^+ retention and volume expansion, contributing to hypertension, as seen in conditions such as Liddle syndrome, Gordon syndrome, and hyperaldosteronism. Conversely, loss-of-function or inhibition of NKCC2, NCC, or ENaC promotes natriuresis and salt-wasting, associated with hypotension and disorders such as Bartter and Gitelman syndromes. Therapeutic interventions targeting these pathways include loop diuretics (NKCC2 inhibitors), thiazide diuretics (NCC inhibitors), ENaC blockers (e.g., amiloride), and mineralocorticoid receptor antagonists that inhibit aldosterone signaling. AQP1, aquaporin-1; AQP2, aquaporin-2; BP, blood pressure; CD, collecting duct; DCT, distal convoluted tubule; ENaC, epithelial sodium channel; NCC, Na^+-Cl^- cotransporter; NHE3, Na^+/H^+ exchanger; NKCC2, Na-K-2Cl cotransporter; OSR1, oxidative stress-responsive kinase 1; RAAS, renin–angiotensin–aldosterone system; ROMK, renal outer medullary potassium; SGLT, sodium-glucose cotransporters; SNS, sympathetic nervous system; SPAK, Ste20-related proline-alanine-rich kinase; TAL, thick ascending limb; WNK, with-no-lysine.

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(NHE3), sodium-glucose cotransporters (SGLT1 and SGLT2), and various sodium–solute cotransport systems [7,8]. SGLT1 is primarily located in the intestinal epithelium and contribute to glucose absorption in the gut while SGLT2 is primarily located in kidney proximal tubule (S1 and S2 segments) and contribute up to 97% of glucose reabsorption in the proximal tubule. SGLT1 in the proximal tubule S2/S3 segments only reabsorb ~3% of glucose in the proximal tubule. Chloride and bicarbonate handling are tightly coupled to sodium transport, and osmotic water reabsorption occurs through aquaporin-1 channels [7,11]. Importantly, proximal tubular sodium transport is modulated by angiotensin II and sympathetic nervous system activity, both of which enhance NHE3 activity and promote volume expansion [6,8]. Genetic or acquired dysregulation of proximal sodium transport alters pressure-natriuresis relationships, thereby contributing to hypertension or, conversely, salt-wasting states [1,3,6].

Loop of Henle

The TAL of the loop of Henle reabsorbs approximately 25% of filtered sodium via the apical NKCC2, functioning as a key site for urinary concentration and medullary gradient formation [1,9]. Potassium recycling through renal outer medullary potassium (ROMK) channels generates a lumen-positive transepithelial voltage that drives paracellular reabsorption of calcium and magnesium [29,30]. Because the TAL is impermeable to water, solute reabsorption without water contributes to dilution of tubular fluid and maintenance of the corticomedullary osmotic gradient [31]. Mutations affecting NKCC2, ROMK, or associated regulatory proteins disrupt sodium reabsorption and typically result in salt wasting and hypotension, as observed in Bartter syndromes [18]. Conversely, enhanced TAL sodium transport increases extracellular volume and elevates blood pressure [3,6]. This segment also participates in tubule-glomerular feedback via macula densa by sensing luminal NaCl and linking tubular electrolyte handling to glomerular hemodynamics and systemic pressure regulation [32,33].

DCT

The DCT reabsorbs approximately 5–10% of filtered sodium, primarily through the thiazide-sensitive Na^+-Cl^- cotransporter (NCC) [10]. Although quantitatively smaller than proximal segments, sodium handling in the DCT exerts disproportionate effects on blood pressure because it lies downstream of the macula densa and is tightly regulated by hormonal and kinase signaling pathways [6,10]. The WNK and its downstream target kinases (Ste20-related proline-alanine-rich kinase [SPAK] and oxidative stress-responsive kinase 1 [OSR1]) play a central role in modulating NCC activity in response to intracellular chloride concentration and hormonal stimuli such as aldosterone and angiotensin II [34]. Gain-of-function mutations in WNK kinases or NCC cause enhanced sodium reabsorption and hypertension, as seen in pseudo-hypoaldosteronism type II (Gordon syndrome), whereas loss-of-function mutations result in Gitelman syndrome with hypotension and hypokalemia [21,22]. Therefore, the DCT represents a critical fine-tuning segment linking electrolyte transport to long-term blood pressure control [6,10].

Collecting duct

The collecting duct is the final regulatory site for sodium, potassium, and water balance, integrating systemic hormonal signals to determine net sodium retention [11,12]. Principal cells mediate sodium reabsorption via ENaC, with basolateral Na^+/K^+-ATPase maintaining the electrochemical gradient. ENaC activity is strongly regulated by aldosterone and modulated by serum- and glucocorticoid-regulated kinase 1 and the E3 ubiquitin ligase neural precursor

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cell expressed, developmentally down-regulated 4-2 (NEDD4-2) [13]. Water permeability in this segment is controlled by vasopressin-dependent insertion of aquaporin-2 channels, linking osmotic regulation to blood pressure [35,36]. Gain-of-function mutations in ENaC result in Liddle syndrome characterized by hypertension and suppressed renin–aldosterone levels, whereas loss-of-function mutations lead to salt-wasting hypotension [13,23]. Through its hormone-sensitive and pressure-responsive properties, the collecting duct serves as a final checkpoint translating electrolyte handling into sustained changes in extracellular volume and arterial pressure [6].

MONOGENIC DISORDERS AFFECTING BLOOD PRESSURE

Bartter syndrome

Bartter syndrome comprises a group of autosomal recessive disorders caused by loss-of-function mutations affecting ion transporters in the TAL of the loop of Henle [14,20]. The most common genetic defects involve *SLC12A1* encoding NKCC2 (type I), *KCNJ1* encoding ROMK (type II), *CLCNKB* encoding ClC-Kb (type III), and *BSND* encoding barttin (type IV) (**Table 1**) [18,37]. These mutations impair NKCC2 or associated potassium recycling and chloride exit across the basolateral membrane [9]. Functionally, reduced NKCC2 activity abolishes lumen-positive transepithelial voltage, leading to diminished paracellular calcium and magnesium reabsorption [38]. The resulting defect in sodium chloride reabsorption produces renal salt wasting, volume contraction, and secondary activation of the RAAS. Despite marked hyperreninemia and hyperaldosteronism, patients typically exhibit normal or low blood pressure due to persistent renal sodium loss [6,37,39]. Clinically, Bartter syndrome is characterized by hypokalemic metabolic alkalosis, hypercalciuria, polyuria, and growth retardation, with antenatal forms presenting as polyhydramnios and premature birth [17,20,37].

Gitelman syndrome

Gitelman syndrome is an autosomal recessive disorder caused by loss-of-function mutations in *SLC12A3*, which encodes the thiazide-sensitive NCC in the DCT (**Table 1**) [17]. Inactivation of NCC reduces sodium and chloride reabsorption in this segment, increasing distal sodium delivery to the collecting duct [10]. Enhanced sodium reabsorption through ENaC in principal cells promotes potassium and hydrogen ion secretion, resulting in hypokalemic metabolic alkalosis. Unlike Bartter syndrome, impaired NCC activity also enhances proximal calcium reabsorption and reduces magnesium uptake in the DCT, leading to hypocalciuria and hypomagnesemia [19,20]. The chronic renal salt wasting induces mild extracellular

Table 1. Monogenic renal tubular disorders: electrolyte abnormalities, blood pressure, and underlying transport defects

Disorder	Affected nephron segment	Subtype	Key transporter (subtype)	Gene	Electrolyte abnormalities	Acid–base status	Blood pressure	Clinical features
Bartter syndrome	Thick ascending limb	I II III IV	NKCC2 ROMK ClC-Kb Barttin	*SLC12A1* *KCNJ1* *CLCNKB* *BSND*	↓ K^+, ↑ Ca^{2+} (hypercalciuria) ± ↓ Mg^{2+}	Metabolic alkalosis	Low/normal	Polyuria, polydipsia, growth retardation, antenatal polyhydramnios
Gitelman syndrome	Distal convoluted tubule		NCC	*SLC12A3*	↓ K^+, ↓ Mg^{2+}, ↓ Ca^{2+} (hypocalciuria)	Metabolic alkalosis	Low/normal	Muscle cramps, fatigue, tetany, chondrocalcinosis
Liddle syndrome	Collecting duct		ENaC	*SCNN1A*, *SCNN1B*, *SCNN1G*	↓ K^+	Metabolic alkalosis	High	Early-onset hypertension, low renin, low aldosterone
Gordon syndrome (PHAII)	Distal convoluted tubule		NCC	*WNK1*, *WNK4*, *KLHL3*, *CUL3*	↑ K^+, normal Ca^{2+}	Metabolic acidosis	High	Hyperkalemia, salt-sensitive hypertension, thiazide-responsive

ENaC, epithelial sodium channel; NCC, Na^+-Cl^- cotransporter; NKCC2, Na-K-2Cl cotransporter; ROMK, renal outer medullary potassium.

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volume contraction and compensatory RAAS activation, yet systemic blood pressure is typically low or normal [18,19]. Clinically, patients present with muscle weakness, cramps, fatigue, tetany, and sometimes chondrocalcinosis in adulthood [40]. The phenotype resembles chronic thiazide diuretic exposure, reflecting the central role of NCC in blood pressure regulation [10,17].

Liddle syndrome

Liddle syndrome is an autosomal dominant form of hypertension caused by gain-of-function mutations in genes encoding subunits of the ENaC, including *SCNN1A*, *SCNN1B*, and *SCNN1G* (**Table 1**) [23,41,42]. Most mutations disrupt the proline-rich PY motif in the β or γ subunit, preventing binding of the ubiquitin ligase NEDD4-2 and thereby impairing ENaC degradation [23,42]. The resulting increase in apical ENaC surface expression enhances sodium reabsorption in principal cells of the collecting duct independent of aldosterone [43]. Increased sodium retention expands extracellular volume and suppresses renin and aldosterone levels, distinguishing Liddle syndrome from other hyperaldosteronism states [23]. Enhanced electrogenic sodium uptake also increases potassium and hydrogen ion secretion, leading to hypokalemic metabolic alkalosis [12]. Clinically, patients develop early-onset hypertension, often severe, with suppressed plasma renin activity and low aldosterone concentrations [42]. The disorder responds to ENaC inhibitors such as amiloride rather than mineralocorticoid receptor antagonists, highlighting its aldosterone-independent mechanism [16,42].

Gordon syndrome (pseudo-hypoaldosteronism type 2)

Gordon syndrome is an autosomal dominant hypertensive disorder characterized by hyperkalemia and metabolic acidosis, resulting from increased sodium chloride reabsorption in the DCT [21]. Causative mutations involve components of the WNK signaling pathway, including *WNK1*, *WNK4*, *KLHL3*, and *CUL3* (**Table 1**) [21,22]. These mutations enhance activation of the WNK–SPAK/OSR1 kinase cascade, leading to increased phosphorylation and activity of NCC [21]. Enhanced NCC-mediated sodium reabsorption reduces distal sodium delivery to the collecting duct, thereby decreasing potassium and hydrogen ion secretion. The net effect is extracellular volume expansion, suppression of renin, and hypertension accompanied by hyperkalemia [44-46]. Unlike Liddle syndrome, aldosterone levels are often normal or mildly elevated but insufficient to overcome the potassium retention caused by reduced distal sodium delivery. Clinically, patients present with familial hypertension, hyperkalemia, and sensitivity to thiazide diuretics, which directly inhibit NCC and correct both blood pressure and electrolyte abnormalities.

GENETIC POLYMORPHISMS IN ION CHANNELS AFFECTING BLOOD PRESSURE

Beyond rare monogenic disorders, common genetic polymorphisms in renal ion channels and their regulatory pathways contribute to interindividual variability in blood pressure within the general population [24-26]. Genome-wide association studies have identified variants in genes encoding sodium transporters and associated signaling molecules—including *SLC12A3* (NCC), *SCNN1A*/*SCNN1G* (ENaC subunits), *WNK1*, and components of the RAAS pathway—that are associated with modest but measurable differences in systolic and diastolic blood pressure [24,26,47]. Unlike pathogenic mutations that markedly disrupt transporter function, these polymorphisms typically induce subtle alterations in channel

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expression, trafficking, or phosphorylation state, thereby slightly shifting tubular sodium reabsorption efficiency. Even small changes in cumulative sodium handling can alter the pressure–natriuresis relationship over time, influencing salt sensitivity and long-term cardiovascular risk [47,48]. Importantly, environmental factors such as dietary sodium intake interact with these genetic variants, highlighting the polygenic and multifactorial nature of essential hypertension. Understanding how common ion channel polymorphisms modulate renal sodium transport may improve risk stratification and enable more personalized antihypertensive strategies.

THERAPEUTIC IMPLICATIONS

Many widely used diuretics target the same transporters implicated in monogenic blood pressure disorders, demonstrating the translational relevance of renal tubular physiology [49]. Loop diuretics inhibit NKCC2 in the TAL, thiazide diuretics target NCC in the DCT, and potassium-sparing agents such as amiloride directly block ENaC in the collecting duct. The clinical phenotypes of Bartter, Gitelman, Liddle, and Gordon syndromes mirror the pharmacologic effects of these agents, providing mechanistic insight into drug responsiveness [50]. For example, patients with Liddle syndrome respond to ENaC inhibition rather than mineralocorticoid receptor antagonists, whereas individuals with Gordon syndrome demonstrate marked sensitivity to thiazide therapy due to NCC hyperactivity.

Beyond rare monogenic conditions, interindividual variability in transporter activity may influence treatment response in essential hypertension [50,51]. Genetic polymorphisms affecting NCC, ENaC, WNK signaling, or RAAS components may partially explain differences in salt sensitivity and diuretic efficacy [50-52]. This raises the possibility of genotype-guided antihypertensive therapy, in which patients with enhanced distal sodium reabsorption preferentially benefit from thiazide or ENaC inhibition, while those with predominant volume expansion may respond more favorably to loop diuretics or RAAS blockade. Furthermore, emerging therapies targeting aldosterone synthase, mineralocorticoid receptor signaling, or novel regulators of the WNK–SPAK pathway may offer more selective modulation of renal sodium handling [53,54].

Taken together, advances in understanding renal ion channel genetics and physiology support a shift toward precision medicine in hypertension, where therapeutic selection is informed not only by blood pressure level but also by the underlying mechanisms of sodium retention and volume regulation [6,26,50].

CONCLUSION

Renal tubular electrolyte handling constitutes the central determinant of blood pressure regulation. Segment-specific sodium transport—from bulk reabsorption in the proximal tubule to fine-tuning in the distal nephron and collecting duct—collectively shapes extracellular volume, pressure–natriuresis dynamics, and systemic arterial pressure. Monogenic disorders such as Bartter, Gitelman, Liddle, and Gordon syndromes provide important evidences demonstrating how discrete alterations in ion channels or their regulatory pathways can shift sodium balance and profoundly influence blood pressure phenotype.

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Beyond rare genetic diseases, common polymorphisms affecting ion transporters and associated signaling networks contribute to interindividual variability in salt sensitivity and hypertension risk. These findings reinforce the concept that essential hypertension is, at least in part, a disorder of renal sodium handling modulated by polygenic and environmental interactions. Importantly, many current antihypertensive therapies directly target the same transport systems implicated in these genetic conditions, highlighting the translational bridge between renal physiology and clinical practice.

Future advances in genomic profiling and phenotyping may enable more precise classification of hypertensive patients based on underlying tubular transport abnormalities. A thorough understanding of ion channel regulation, intracellular signaling pathways, and gene–environment interactions will be essential for the development of personalized therapeutic strategies. Ultimately, integrating renal physiology, genetics, and clinical medicine offers a path toward mechanism-based management of blood pressure and improved cardiovascular outcomes.

REFERENCES

1. Guyton AC. Blood pressure control—special role of the kidneys and body fluids. *Science* 1991;252:1813-1816. PUBMED | CROSSREF
2. Guyton AC, Coleman TG, Cowley AV Jr, Scheel KW, Manning RD Jr, Norman RA Jr. Arterial pressure regulation. Overriding dominance of the kidneys in long-term regulation and in hypertension. *Am J Med* 1972;52:584-594. PUBMED | CROSSREF
3. Cowley AW Jr, Roman RJ. The role of the kidney in hypertension. *JAMA* 1996;275:1581-1589. PUBMED | CROSSREF
4. Hamlyn JM, Blaustein MP. Sodium chloride, extracellular fluid volume, and blood pressure regulation. *Am J Physiol* 1986;251:F563-F575. PUBMED | CROSSREF
5. Danziger J, Hoenig MP. The role of the kidney in disorders of volume: core curriculum 2016. *Am J Kidney Dis* 2016;68:808-816. PUBMED | CROSSREF
6. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. *Cell* 2001;104:545-556. PUBMED | CROSSREF
7. Curthoys NP, Moe OW. Proximal tubule function and response to acidosis. *Clin J Am Soc Nephrol* 2014;9:1627-1638. PUBMED | CROSSREF
8. McDonough AA. Mechanisms of proximal tubule sodium transport regulation that link extracellular fluid volume and blood pressure. *Am J Physiol Regul Integr Comp Physiol* 2010;298:R851-R861. PUBMED | CROSSREF
9. Castrop H, Schießl IM. Physiology and pathophysiology of the renal Na-K-2Cl cotransporter (NKCC2). *Am J Physiol Renal Physiol* 2014;307:F991-F1002. PUBMED | CROSSREF
10. Subramanya AR, Ellison DH. Distal convoluted tubule. *Clin J Am Soc Nephrol* 2014;9:2147-2163. PUBMED | CROSSREF
11. Zeidel ML. Hormonal regulation of inner medullary collecting duct sodium transport. *Am J Physiol* 1993;265:F159-F173. PUBMED | CROSSREF
12. Stokes JB. Sodium and potassium transport by the collecting duct. *Kidney Int* 1990;38:679-686. PUBMED | CROSSREF
13. Schafer JA. Abnormal regulation of ENaC: syndromes of salt retention and salt wasting by the collecting duct. *Am J Physiol Renal Physiol* 2002;283:F221-F235. PUBMED | CROSSREF
14. Zelikovic I. Molecular pathophysiology of tubular transport disorders. *Pediatr Nephrol* 2001;16:919-935. PUBMED | CROSSREF
15. Hamilton KL, Butt AG. The molecular basis of renal tubular transport disorders. *Comp Biochem Physiol A Mol Integr Physiol* 2000;126:305-321. PUBMED | CROSSREF
16. Scheinman SJ, Guay-Woodford LM, Thakker RV, Warnock DG. Genetic disorders of renal electrolyte transport. *N Engl J Med* 1999;340:1177-1187. PUBMED | CROSSREF

17. Simon DB, Karet FE, Hamdan JM, Di Pietro A, Sanjad SA, Lifton RP. Bartter's syndrome, hypokalaemic alkalosis with hypercalciuria, is caused by mutations in the Na-K-2Cl cotransporter NKCC2. *Nat Genet* 1996;13:183-188. PUBMED | CROSSREF

18. Simon DB, Lifton RP. Ion transporter mutations in Gitelman's and Bartter's syndromes. *Curr Opin Nephrol Hypertens* 1998;7:43-47. PUBMED | CROSSREF

19. Knoers NV, Levtchenko EN. Gitelman syndrome. *Orphanet J Rare Dis* 2008;3:22. PUBMED | CROSSREF

20. Seyberth HW. An improved terminology and classification of Bartter-like syndromes. *Nat Clin Pract Nephrol* 2008;4:560-567. PUBMED | CROSSREF

21. Wilson FH, Disse-Nicodème S, Choate KA, et al. Human hypertension caused by mutations in WNK kinases. *Science* 2001;293:1107-1112. PUBMED | CROSSREF

22. Boyden LM, Choi M, Choate KA, et al. Mutations in kelch-like 3 and cullin 3 cause hypertension and electrolyte abnormalities. *Nature* 2012;482:98-102. PUBMED | CROSSREF

23. Yang KQ, Xiao Y, Tian T, Gao LG, Zhou XL. Molecular genetics of Liddle's syndrome. *Clin Chim Acta* 2014;436:202-206. PUBMED | CROSSREF

24. Ehret GB. Genome-wide association studies: contribution of genomics to understanding blood pressure and essential hypertension. *Curr Hypertens Rep* 2010;12:17-25. PUBMED | CROSSREF

25. Padmanabhan S, Caulfield M, Dominiczak AF. Genetic and molecular aspects of hypertension. *Circ Res* 2015;116:937-959. PUBMED | CROSSREF

26. Evangelou E, Warren HR, Mosen-Ansorena D, et al. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. *Nat Genet* 2018;50:1412-1425. PUBMED | CROSSREF

27. Gu X, Gu D, He J, et al. Resequencing epithelial sodium channel genes identifies rare variants associated with blood pressure salt-sensitivity: the GenSalt study. *Am J Hypertens* 2018;31:205-211. PUBMED | CROSSREF

28. Huan T, Esko T, Peters MJ, et al. A meta-analysis of gene expression signatures of blood pressure and hypertension. *PLoS Genet* 2015;11:e1005035. PUBMED | CROSSREF

29. Gamba G, Friedman PA. Thick ascending limb: the Na^+:K^+:$2Cl^-$ co-transporter, NKCC2, and the calcium-sensing receptor, CaSR. *Pflugers Arch* 2009;458:61-76. PUBMED | CROSSREF

30. Zacchia M, Capolongo G, Rinaldi L, Capasso G. The importance of the thick ascending limb of Henle's loop in renal physiology and pathophysiology. *Int J Nephrol Renovasc Dis* 2018;11:81-92. PUBMED | CROSSREF

31. Dantzler WH, Layton AT, Layton HE, Pannabecker TL. Urine-concentrating mechanism in the inner medulla: function of the thin limbs of the loops of Henle. *Clin J Am Soc Nephrol* 2014;9:1781-1789. PUBMED | CROSSREF

32. Schnermann J, Briggs JP. Tubuloglomerular feedback: mechanistic insights from gene-manipulated mice. *Kidney Int* 2008;74:418-426. PUBMED | CROSSREF

33. Edwards A, Castrop H, Laghmani K, Vallon V, Layton AT. Effects of NKCC2 isoform regulation on NaCl transport in thick ascending limb and macula densa: a modeling study. *Am J Physiol Renal Physiol* 2014;307:F137-F146. PUBMED | CROSSREF

34. Richardson C, Rafiqi FH, Karlsson HK, et al. Activation of the thiazide-sensitive Na^+-Cl^- cotransporter by the WNK-regulated kinases SPAK and OSR1. *J Cell Sci* 2008;121:675-684. PUBMED | CROSSREF

35. Wilson JL, Miranda CA, Knepper MA. Vasopressin and the regulation of aquaporin-2. *Clin Exp Nephrol* 2013;17:751-764. PUBMED | CROSSREF

36. Schrier RW. Vasopressin and aquaporin 2 in clinical disorders of water homeostasis. *Semin Nephrol* 2008;28:289-296. PUBMED | CROSSREF

37. Florea L, Caba L, Gorduza EV. Genetic heterogeneity in Bartter syndrome: clinical and practical importance. *Front Pediatr* 2022;10:908655. PUBMED | CROSSREF

38. Al Shibli A, Narchi H. Bartter and Gitelman syndromes: spectrum of clinical manifestations caused by different mutations. *World J Methodol* 2015;5:55-61. PUBMED | CROSSREF

39. Mrad FCC, Soares SBM, de Menezes Silva LAW, Dos Anjos Menezes PV, Simões-E-Silva AC. Bartter's syndrome: clinical findings, genetic causes and therapeutic approach. *World J Pediatr* 2021;17:31-39. PUBMED | CROSSREF

40. Cruz DN, Shaer AJ, Bia MJ, Lifton RP, Simon DB; Yale Gitelman's and Bartter's Syndrome Collaborative Study Group. Gitelman's syndrome revisited: an evaluation of symptoms and health-related quality of life. *Kidney Int* 2001;59:710-717. PUBMED | CROSSREF

41. Hansson JH, Nelson-Williams C, Suzuki H, et al. Hypertension caused by a truncated epithelial sodium channel γ subunit: genetic heterogeneity of Liddle syndrome. *Nat Genet* 1995;11:76-82. PUBMED | CROSSREF

42. Tetti M, Monticone S, Burrello J, et al. Liddle syndrome: review of the literature and description of a new case. *Int J Mol Sci* 2018;19:812. PUBMED | CROSSREF

43. Knight KK, Olson DR, Zhou R, Snyder PM. Liddle's syndrome mutations increase Na^+ transport through dual effects on epithelial Na^+ channel surface expression and proteolytic cleavage. *Proc Natl Acad Sci U S A* 2006;103:2805-2808. PUBMED | CROSSREF

44. Cornelius RJ, Maeoka Y, Shinde U, McCormick JA. Familial hyperkalemic hypertension. *Compr Physiol* 2024;14:5839-5874. PUBMED | CROSSREF

45. Rafael C, Hadchouel J. Familial Hyperkalemic Hypertension (FHHt). In: Caprio M, Fernandes-Rosa FL, eds. Hydro Saline Metabolism: Epidemiology, Genetics, Pathophysiology, Diagnosis and Treatment. Springer; 2023. p. 97-139.

46. Hadchouel J, Delaloy C, Fauré S, Achard JM, Jeunemaitre X. Familial hyperkalemic hypertension. *J Am Soc Nephrol* 2006;17:208-217. PUBMED | CROSSREF

47. An C, Yang L, Han T, et al. Kidney ion handling genes and their interaction in blood pressure control. *Biosci Rep* 2022;42:BSR20220977. PUBMED | CROSSREF

48. Ji W, Foo JN, O'Roak BJ, et al. Rare independent mutations in renal salt handling genes contribute to blood pressure variation. *Nat Genet* 2008;40:592-599. PUBMED | CROSSREF

49. Ellison DH. Clinical pharmacology in diuretic use. *Clin J Am Soc Nephrol* 2019;14:1248-1257. PUBMED | CROSSREF

50. Vormfelde SV, Burckhardt G, Zirk A, Wojnowski L, Brockmöller J. Pharmacogenomics of diuretic drugs: data on rare monogenic disorders and on polymorphisms and requirements for further research. *Pharmacogenomics* 2003;4:701-734. PUBMED | CROSSREF

51. Cooper-DeHoff RM, Johnson JA. Hypertension pharmacogenomics: in search of personalized treatment approaches. *Nat Rev Nephrol* 2016;12:110-122. PUBMED | CROSSREF

52. Vormfelde SV, Sehrt D, Toliat MR, et al. Genetic variation in the renal sodium transporters NKCC2, NCC, and ENaC in relation to the effects of loop diuretic drugs. *Clin Pharmacol Ther* 2007;82:300-309. PUBMED | CROSSREF

53. Ferdaus MZ, McCormick JA. The CUL3/KLHL3-WNK-SPAK/OSR1 pathway as a target for antihypertensive therapy. *Am J Physiol Renal Physiol* 2016;310:F1389-F1396. PUBMED | CROSSREF

54. Brown A, Meor Azlan NF, Wu Z, Zhang J. WNK-SPAK/OSR1-NCC kinase signaling pathway as a novel target for the treatment of salt-sensitive hypertension. *Acta Pharmacol Sin* 2021;42:508-517. PUBMED | CROSSREF

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Review Article

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Integrating Blood Pressure Control With Multi-Class Kidney Protective Agents in Diabetic Kidney Disease

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ABSTRACT

Diabetic kidney disease (DKD) remains a leading cause of chronic kidney disease progression and cardiovascular morbidity and mortality. Blood pressure (BP) control is a cornerstone of risk reduction in DKD, yet its management has become increasingly complex with the emergence of multi-class kidney-protective agents. Traditionally centered on renin-angiotensin-aldosterone system (RAAS) blockade with additional antihypertensive agents, contemporary treatment now incorporates sodium-glucose cotransporter-2 (SGLT2) inhibitors, non-steroidal mineralocorticoid receptor antagonists, and incretin-based therapies. Recent trials evaluating intensive systolic BP targets have demonstrated cardiovascular benefit in selected high-risk populations; however, the balance between benefit and kidney-related harm remains relevant in DKD. While RAAS blockade provides meaningful BP reduction and renoprotection, SGLT2 inhibitors, finerenone, and incretin-based therapies confer modest but clinically relevant BP lowering alongside substantial cardiorenal benefits through complementary mechanisms. Although these agents are not primarily used for antihypertensive intensification, their meaningful BP-lowering effects can influence overall BP control in routine practice. Although combination therapy appears biologically plausible and may enhance overall cardio-kidney-metabolic protection, definitive evidence supporting optimal sequencing, parallel initiation, or superiority in hard clinical outcomes remains limited. A pragmatic, individualized approach integrating disease-modifying therapies with conventional antihypertensive agents is therefore warranted. Future dedicated trials are needed to clarify optimal integration strategies to achieve safe BP control while maximizing long-term kidney and cardiovascular protection in DKD.

Keywords: Diabetic kidney disease; Glucagon-like peptide-1 receptor agonists; Hypertension; Mineralocorticoid receptor antagonists; Renin-angiotensin-aldosterone system; Sodium-glucose transporter 2 inhibitors

INTRODUCTION

Diabetic kidney disease (DKD) remains a leading cause of chronic kidney disease (CKD) progression and end-stage kidney disease and it is strongly associated with excess cardiovascular morbidity and mortality [1]. Among the various modifiable risk factors in

DKD, control of blood pressure (BP) and glucose are consistently recognized as key factors to reduce albuminuria progression, decline in glomerular filtration rate, and adverse cardiovascular outcomes [2,3].

Over the past decade, the management of DKD has undergone a major paradigm shift. Traditionally, BP control has been achieved primarily through renin-angiotensin-aldosterone system (RAAS) blockade as the cornerstone of pharmacologic treatment with additional antihypertensive agents as needed, whereas glycemic control has relied on glucose-lowering agents as a separate domain. However, therapeutic landscape has rapidly expanded with the emergence of multi-class kidney-protective agents, including sodium-glucose cotransporter-2 (SGLT2) inhibitors, mineralocorticoid receptor antagonists (MRAs) such as finerenone, and incretin-based therapies such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) [4-10]. Beyond their primary indications (e.g., glycemic control and weight reduction), these agents commonly provide a modest but consistent BP-lowering effect. Consequently, BP management in DKD is no longer solely dependent on conventional antihypertensive agents, and clinicians now have an expanding range of therapeutic options that can simultaneously address BP, glucose, and other metabolic risk factors that lead to long-term cardiorenal protection. In other words, the clinical challenge has evolved from simply "adding more BP-lowering agents" to making individualized decisions based on patients' characteristics and comorbidities. At the same time, their adverse-effect profiles and monitoring requirements differ substantially, particularly with regard to volume status changes, kidney function dynamics, gastrointestinal tolerability, and the risk of hyperkalemia [11-13]. Collectively, the key questions in real-world clinics to manage DKD is how clinicians can strategically select and combine multi-class kidney-protective therapies to achieve safe BP target while maximizing overall clinical benefit.

In contemporary clinical practice, multi-class kidney-protective agents are not primarily initiated for BP lowering. However, BP reduction effects of these agents may influence overall BP control and necessitate adjustment of concomitant antihypertensive medications. Therefore, understanding the magnitude and characteristics of BP-lowering effects of each therapeutic class has important implications for real-world treatment strategies. In this review, we aim to provide a practical framework for integrating these therapies by clarifying their relative contributions to BP reduction in DKD. We summarize contemporary BP targets in guidelines, review foundational background therapies, including RAAS blockade and SGLT2 inhibitors, and then focus on newer agents such as finerenone and incretin-based therapies, highlighting their distinct cardiorenal benefits, safety profiles, and monitoring needs.

BP TARGETS IN DKD

For the last decade, there has been a trend toward more intensive BP control for hypertensive patients, whereas the optimal BP target in DKD remains an area of active debate. The landmark SPRINT trial compared an intensive systolic blood pressure (SBP) target (< 120 mmHg) with a standard target (< 140 mmHg) in high-risk hypertensive adults and showed significant reductions in major cardiovascular events and all-cause mortality with intensive treatment [14]. However, this study excluded patients with diabetes. In contrast, the ACCORD-BP trial, which specifically enrolled patients with type 2 diabetes, did not show a significant reduction in the primary composite cardiovascular outcome with intensive SBP targeting < 120 mmHg compared with < 140 mmHg, although stroke risk was reduced

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at the expense of more adverse events [15]. However, more recent ESPRIT trial enrolled patients at high cardiovascular risk, with and without diabetes or prior stroke, and compared SBP targets of < 120 versus < 140 mmHg [16]. Likewise, the BPROAD trial focused on patients with type 2 diabetes and evaluated intensive SBP lowering toward < 120 mmHg [17]. Together, these trials have reinforced the concept that intensive SBP lowering can translate into cardiovascular benefit in selective patients with type 2 diabetes.

Nevertheless, in DKD, the clinical dilemma is not simply whether intensive BP lowering can improve cardiovascular outcomes, but whether pursuing SBP < 120 mmHg is always necessary when kidney-related harms are explicitly considered. This question is particularly relevant in DKD because patients often have heightened hemodynamic vulnerability due to reduced nephron reserve, frequent diuretic exposure, autonomic dysfunction. Consequently, very intensive BP lowering may be accompanied by kidney-related adverse effects even when long-term cardiovascular benefit is anticipated [18]. A recent meta-analysis pooled six pivotal intensive BP trials (ACCORD-BP, SPRINT, ESPRIT, BPROAD, STEP, and CRHCP) and quantified this benefit-harm trade-off, demonstrating that intensive BP control reduced major cardiovascular events while increasing adverse events of interest, including kidney-related outcomes (acute kidney injury, renal failure, kidney failure/dialysis, or substantial estimated glomerular filtration rate [eGFR] decline) [19]. Importantly, when outcomes were further analyzed by SBP target category (< 120 mmHg vs. < 130 mmHg), the absolute cardiovascular risk reduction with intensive treatment was numerically greater in the < 120 mmHg target (1.84%, 95% confidence interval [CI], 1.75–1.92) than in the < 130 mmHg target (1.65%, 1.54–1.76). However, when harms were incorporated using adjudicated benefit-to-harm weights, net benefit versus total adverse events of interest was 0.97 (0.87–1.06) for < 120 mmHg target and 1.27 (1.16–1.37) for < 130 mmHg target, while net benefit versus kidney-related adverse events was 0.77 (0.59–0.92) for < 120 mmHg target versus 1.43 (1.32–1.53) for < 130 mmHg target. These findings suggest that although more intensive SBP lowering toward < 120 mmHg may yield incremental cardiovascular risk reduction, a pragmatic SBP target < 130 mmHg may offer a more favorable benefit-harm balance, particularly when kidney-related harms are explicitly weighed, an issue of heightened relevance in DKD.

Current guidelines reflect both the momentum toward lower BP targets and the need for cautious implementation. The 2021 Kidney Disease: Improving Global Outcomes (KDIGO) BP guideline recommends treating adults with CKD and hypertension to SBP < 120 mmHg (when tolerated), but critically specifies that this target should be applied only with standardized office BP measurement, acknowledging the gap between trial-grade measurement and routine clinic BP values [20]. More recent 2022 Korean Society of Hypertension BP guideline also emphasizes the importance of office BP measurement with standardized method, but also recommends to use out-of-office BP measurements, such as ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM) for diagnosis and monitoring of hypertension [21,22]. Additionally, the KSH guideline supports targeting < 130/80 mmHg in high-risk individuals, including patients with diabetes plus additional cardiovascular risk factors or those with CKD accompanied by albuminuria, to balance between clinical benefit and masked side effects during intensive BP control [23]. Most recently, the 2025 American College of Cardiology (ACC)/American Heart Association (AHA)/Multisociety BP guideline provides a broadly applicable target of < 130/80 mmHg for most adults, reinforcing the importance of early treatment and intensification in high-risk conditions such as diabetes and CKD [24]. However, the ACC/AHA guideline encourages to achieve lower SBP targets (approaching < 120 mmHg) selectively in case of well-tolerable

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patients with diabetes. Taken together, these recommendations support a pragmatic DKD strategy in which < 130/80 mmHg serves as a broadly implementable default target, while SBP < 120 mmHg is reserved for carefully selected individuals with very high cardiovascular risk, reliable standardized (and/or out-of-office) BP assessment, and good treatment tolerability.

BACKGROUND BP MANAGEMENT WITH CLASSICAL ANTIHYPERTENSIVE AGENTS IN DKD

RAAS blockade remains a foundational component of BP management in DKD, primarily because of its well-established renoprotective effect [25-27]. Accordingly, abovementioned BP guidelines consistently recommend to use of RAAS blockade as first-line therapy to treat hypertension in patients with DKD, especially when patients have albuminuria [20,23,24]. In terms of BP reduction *per se*, a large systematic review and meta-analysis, which pooled 484 randomized controlled trials (RCTs), demonstrated that standard-dose monotherapy reduced SBP by an average of 6.8 mmHg (95% CI, 5.9–7.7) for angiotensin-converting enzyme (ACE) inhibitors and 8.5 mmHg (7.8–9.3) for angiotensin II receptor blockers (ARBs) [28]. Moreover, doubling the dose of monotherapy resulted in only a modest additional SBP reduction of approximately 1–2 mmHg, supporting the notion that RAAS blockade monotherapy may not enough to achieve BP target in most patients. Meanwhile, evidence specific to CKD further refines this interpretation. In a systematic review and meta-analysis of 24 RCTs focusing on patients with concomitant hypertension and CKD, ARB monotherapy reduced SBP by approximately 12–15 mmHg and diastolic BP by 6–10 mmHg, with numerically greater reductions observed with longer treatment duration [29].

Additionally, both meta-analyses consistently demonstrate that combination therapy is substantially more effective than dose escalation of a single agent. Among the classical antihypertensive agents, calcium channel blockers (CCBs) and thiazide or thiazide-like diuretics are the most commonly selected second-line options. In the same large-scale meta-analysis of 484 RCTs, standard-dose CCB monotherapy was associated with a mean SBP reduction of approximately 8–11 mmHg, and thiazide-type diuretics achieved SBP reductions of approximately 9–12 mmHg from comparable baseline BP levels [28]. High-quality RCTs specifically designed to optimal second-line choice in DKD remain limited, but several influential studies provide important insights. In a large trial with hypertensive patients with a high-risk of cardiovascular disease (CVD), an ACE inhibitor combined with a dihydropyridine CCB was superior to the same ACE inhibitor combined with a thiazide diuretic in reducing cardiovascular events, despite similar achieved BP levels [30]. Subsequent analyses also suggested less progression of CKD in the CCB-based group, supporting the use of CCBs as a second-line agent when CVD risk reduction is a primary therapeutic goal [31]. Conversely, a recent CKD-focused observational study suggests that diuretics may offer advantages [32]. This study including moderate to advanced CKD patients have reported comparable cardiovascular outcomes but potentially more favorable kidney outcomes when diuretics were added to background RAAS blockade, compared with CCBs-based combinations. These findings are biologically plausible, given the increasing contribution of sodium retention and volume expansion to hypertension as kidney function declines. In contrast, previous trials have shown that combination of RAAS blockades increases the risk of hyperkalemia and acute kidney injury [33,34]. Therefore, combination of RAAS blockade is not recommend as a BP-lowering strategy.

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POSITIONING SGLT2 INHIBITORS AS SECOND-LINE THERAPY AFTER RAAS BLOCKADE

Meanwhile, with the advent of SGLT2 inhibitors, the traditional paradigm of selecting CCBs or diuretics as second-line therapy after RAAS blockade for BP-lowering in DKD warrants reconsideration. Although SGLT2 inhibitors were initially developed as glucose-lowering agents, multiple large-scale outcome trials have consistently demonstrated substantial kidney and cardiovascular benefits in patients with DKD, most of whom were receiving background RAAS blockade [4,5,35]. In addition, a recent meta-analysis showed that protective effect of SGLT2 inhibitor for CKD progression was consistent across almost all range of eGFR and albuminuria categories [36]. Accordingly, current KDIGO guidelines commonly recommend the use of SGLT2 inhibitors in all CKD patients with eGFR greater than 20 mL/min/1.73 m^2 [3,37], positioning SGLT2 inhibitors as foundational therapy in contemporary DKD management.

From a BP-lowering perspective, SGLT2 inhibitors exert a modest but consistent antihypertensive effect, with meta-analyses reporting an average SBP reduction of approximately 3–5 mmHg compared with placebo [38,39]. However, accumulating evidence suggests that this effect is highly heterogeneous and strongly influenced by patient phenotype. Greater BP reductions have been observed in individuals with higher baseline BP, obesity, salt sensitivity, and features of volume expansion, as well as in those with uncontrolled nocturnal or masked hypertension despite background RAAS blockade [40]. Studies using ABPM or HBPM further indicate that SGLT2 inhibitors may preferentially lower 24-hour, nighttime, and early morning BP rather than office BP, thereby improving adverse circadian BP patterns that are common in patients with diabetes and CKD [41]. In selected populations, including elderly patients, East Asian cohorts, and those with resistant or nocturnal hypertension, SBP reductions exceeding 7–10 mmHg have been reported [42,43].

Taken together, these data support that the combination of RAAS blockade and an SGLT2 inhibitor may be sufficient to achieve guideline-recommended BP targets in a subset of patients with DKD. However, given the modest and variable magnitude of BP reduction associated with SGLT2 inhibitors, a substantial proportion of patients will require additional antihypertensive therapy to reach BP goals. At the same time, the use of SGLT2 inhibitors necessitates careful attention to safety and tolerability. Adverse effects such as volume depletion, genital infections, and diabetic ketoacidosis may limit their use in selected patients, particularly in those receiving concomitant diuretic therapy or in older patients with frailty and sarcopenia [11,44-46]. Accordingly, initiation of SGLT2 inhibitors should be accompanied by assessment of volume status, consideration of diuretic dose adjustment, and close clinical monitoring.

NON-STEROIDAL MRAS AND BP CONTROL IN DKD

Non-steroidal MRAs, represented by finerenone, have emerged as an important disease-modifying therapy in DKD. Previous two large clinical trials, FIGARO-DKD and FIDELIO-DKD, encompassing a broad spectrum of DKD patients with eGFR greater than 25 mL/min/1.73 m^2 with albuminuria have shown that finerenone significantly reduced the risks of CKD progression and cardiovascular events compared with placebo on a background of optimized RAAS blockade [6,7,47]. Reflecting this body of evidence, finerenone has

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been incorporated into contemporary 2022 KDIGO guideline for diabetes management in CKD as an add-on therapy for patients with type 2 diabetes and CKD who have persistent albuminuria despite optimized RAAS blockade [3].

However, from a BP perspective, finerenone produces a modest reduction in BP. In previous trials, finerenone lowered office SBP by approximately 2–4 mmHg compared with placebo [6,7], which is smaller than that observed with traditional steroidal MRAs. In comparative analyses involving patients with resistant hypertension and moderate-to-advanced CKD, finerenone was associated with a smaller reduction in SBP than spironolactone [48]. While spironolactone achieved greater BP reductions, this benefit was offset by markedly higher rates of potassium elevation and drug discontinuation, even when combined with potassium-binding agents. Mediation analyses further demonstrated that BP lowering accounted for only a small proportion of the observed kidney and cardiovascular benefits, indicating that finerenone's therapeutic effects are largely mediated through non-hemodynamic mechanisms, including attenuation of mineralocorticoid receptor-driven inflammation and fibrosis [49]. Thus, in contrast to steroidal MRAs such as spironolactone, which are often used for resistant hypertension due to their substantial BP-lowering effects, the clinical value of finerenone in DKD lies predominantly in its disease-modifying effects, with BP reduction serving as an ancillary benefit. However, recent clinical trial provided randomized evidence regarding the BP lowering effect of combined use of finerenone and an SGLT2 inhibitor. In patients with DKD receiving background RAAS blockade, combination therapy with finerenone and empagliflozin resulted in a greater early reduction in albuminuria and a transiently larger reduction in SBP, approximately 7 mmHg within the first month, compared with either agent alone, without an excess risk of symptomatic hypotension or acute kidney injury [50].

When initiating finerenone, careful attention to adverse effects and monitoring is essential. Hyperkalemia remains the principal safety concern, although its incidence and severity are substantially lower than those observed with steroidal MRAs. Current clinical practice therefore requires routine monitoring of serum potassium and kidney function, particularly after treatment initiation or dose escalation and in patients with advanced CKD.

INCRETIN-BASED THERAPIES AND BP CONTROL IN DKD

Incretin-based therapies, most notably GLP-1 RAs and more recently dual incretin agonists such as tirzepatide, have become increasingly relevant in DKD. In patients with type 2 diabetes and CKD, the FLOW trial demonstrated that once-weekly semaglutide reduced clinically important kidney outcomes and cardiovascular death compared with placebo, supporting GLP-1 RAs as disease-modifying therapies in DKD [8]. In addition, recent evidence also showed that tirzepatide was associated with a sustained reduction in albuminuria without adverse effects on eGFR in participants with overweight or obesity with type 2 diabetes [51]. Importantly, incretin-based therapies have shown to reduce the risk of atherosclerotic CVD accompanied by improvements in body weight, glycemic control, and lipid profiles [52]. Collectively, these data position incretin-based therapies as adjunctive agents that can contribute cardiometabolic and renal benefits in patients with DKD, particularly those with overweight or obesity.

The FLOW trial showed a modest reduction in SBP (3.8 mmHg) with semaglutide which an achieved SBP difference of approximately 2 mmHg compared with placebo [8]. A recent

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meta-analysis of semaglutide trials reported that SBP lowering effect of semaglutide was 3–5 mmHg in hypertensive patients with obesity, and mediation analysis suggested that nearly 90% of SBP reduction was attributable to weight loss in this population [53]. Similarly, post-hoc analyses of five clinical trials of tirzepatide reported dose-dependent SBP and body weight reductions, and maximum dose of tirzepatide was associated with SBP reduction of up to 11 mmHg in patient with obesity, indicating that SBP reduction of tirzepatide was primarily mediated by weight loss [54]. These findings suggest that in patients with DKD, BP reduction with incretin-based therapies may be more clinically relevant in those with obesity, with BP reduction serving as a secondary and modest effect. Beyond weight loss, experimental studies suggest that incretin-based therapies may contribute to BP lowering through additional pathways, including attenuation of sympathetic nervous system activity, improvement in endothelial function, and promotion of natriuresis in the kidney [55]. However, careful attention to tolerability is required, as gastrointestinal adverse effects (nausea, vomiting, and diarrhea) may precipitate volume depletion and worsen kidney function, particularly in patients receiving concomitant diuretics or SGLT2 inhibitors. Additional safety considerations include the potential risk of gallbladder disease, and the need for caution in patients with a history of pancreatitis or advanced diabetic retinopathy during rapid glycemic improvement.

Meanwhile, because both SGLT2 inhibitors and incretin-based therapies provide substantial cardiorenal benefit, there has been growing interest in whether their combined use can further improve outcomes. Although recent observational study showed lower risks of CVD and renal events with this combination [56], definitive evidence from dedicated head-to-head RCTs remained limited, and it is still uncertain whether combined therapy provides incremental benefit beyond either class alone for hard clinical endpoints [57]. From BP perspective, a meta-analysis of seven RCTs showed that combination of GLP-1 RAs and SGLT2 inhibitors lowered SBP compared with GLP-1 RAs alone (−2.6 mmHg) or SGLT2 inhibitors alone (−1.5 mmHg) [58]. However, these trials were short-term, not specifically designed for DKD populations, and often included heterogeneous background antihypertensive regimens. Therefore, while dual therapy is biologically plausible and may offer modest incremental BP lowering through complementary mechanisms, natriuresis and plasma volume contraction (SGLT2 inhibitors) together with weight loss and neurovascular effects (GLP-1 RAs), the magnitude and durability of BP benefit in DKD remain uncertain. Collectively, with current evidence, although BP reduction alone should not be the primary rationale for combination therapy, combined use should be considered mainly to strengthen overall cardio-kidney-metabolic protection, with BP effects viewed as an ancillary benefit.

PRACTICAL INTEGRATION OF MULTI-CLASS KIDNEY-PROTECTIVE AND ANTIHYPERTENSIVE AGENTS FOR BP CONTROL IN DKD

BP management in DKD should be approached through a pragmatic framework that integrates multi-class kidney-protective therapies with conventional antihypertensive agents (**Table 1**). Therapies used in DKD can be broadly categorized into two groups: agents primarily used for antihypertensive intensification (RAAS blockades, CCBs, diuretics), and disease-modifying therapies that confer cardio-renal protection with modest or secondary BP-lowering effects (SGLT2 inhibitors, finerenone, incretin-based therapies). Optimized

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Table 1. Practical integration of multi-class kidney-protective agents for BP control in diabetic kidney disease

Agent class	Typical position	Expected SBP reduction (approx.)	Key determinants of BP response	Safety monitoring/key cautions
Background agents				
RAAS blockade (ACEi or ARB)	First-line (foundational)	7–9 mmHg	Baseline BP, sodium intake	Serum creatinine/eGFR and potassium after initiation and dose escalation
Add-on kidney-protective agents				
SGLT2 inhibitors	Early second-line/ background therapy	3–5 mmHg (up to 7–10 mmHg in selected patients)	Volume status, baseline BP, salt sensitivity, nocturnal/masked HTN	Genital infections, rare DKA, volume status
Non-steroidal MRA (finerenone)	Add-on for persistent albuminuria	2–4 mmHg	Baseline BP, RAAS background therapy	Potassium and kidney function monitoring
GLP-1 RAs/dual incretin agonists	Add-on for obesity and high risk of CVD	2–5 mmHg (up to 10–11 mmHg in obesity)	Body weight change, baseline BP, metabolic profile	GI intolerance, gallbladder disease, pancreatitis, rare retinopathy
Add-on antihypertensive agents				
Calcium channel blockers	Add-on when BP remains above target	8–11 mmHg	Vascular tone, baseline BP	Peripheral edema, headache
Diuretics (thiazide/thiazide-like or loop)	Add-on when BP remains above target and volume expansion present	9–12 mmHg	Volume status, kidney function, sodium intake	Electrolyte imbalance, volume depletion, gout

The estimated SBP reductions presented in this table are derived from different clinical trials with heterogeneous populations, study designs, background therapies, and follow-up durations. Therefore, these values should be interpreted as approximate reference ranges rather than directly comparable estimates.
ARB, angiotensin II receptor blocker; ACEi, angiotensin-converting enzyme inhibitor; BP, blood pressure; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; GI, gastrointestine; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HTN, hypertension; MRA, mineralocorticoid receptor antagonist; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter 2.

RAAS blockade remains foundational first-line therapy, particularly in albuminuric DKD. Following RAAS blockade, early initiation of an SGLT2 inhibitor is increasingly viewed as background therapy, given its robust cardiorenal benefits and modest SBP lowering. In patients with persistent albuminuria despite background therapy, add-on kidney-protective agents may be considered. Finerenone provides modest SBP reduction with predominantly non-hemodynamic cardiorenal benefits. Incretin-based therapies may be particularly useful in patients with obesity or high cardiovascular risk, offering modest and largely weight-mediated SBP reduction alongside substantial cardiometabolic benefit.

When BP remains above target, conventional antihypertensive agents, most commonly CCBs or diuretics, remain essential and should be selected according to clinical phenotype and volume status. Overall, this approach emphasizes early use of disease-modifying therapies and individualized antihypertensive intensification. However, it remains uncertain whether these agents should be introduced sequentially or in parallel, and which combinations are optimal. Moreover, there is still no definitive evidence that combination strategies improve hard clinical outcomes compared with single-class therapy.

CONCLUSIONS

BP control remains a central component of risk reduction in DKD, yet its management has become increasingly complex in the era of multi-class kidney-protective therapies. Although these agents are not primarily used for antihypertensive intensification, they exert modest but clinically meaningful BP-lowering effects that may influence overall BP control in routine practice. Despite the growing role of disease-modifying therapies, conventional antihypertensive agents such as CCBs and diuretics remain essential for achieving BP targets. Accordingly, clinicians should recognize that initiation of kidney-protective therapies may require adjustment of conventional antihypertensive medications to achieve optimal

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BP targets while minimizing adverse effects. A practical approach therefore requires careful integration of disease-modifying therapies with conventional antihypertensive agents based on individual patient characteristics. Although combination therapy of kidney-protective agents appears biologically plausible and may enhance overall risk reduction, definitive evidence supporting specific sequencing strategies or superiority in hard clinical outcomes remains limited. Future trials are needed to clarify optimal integration strategies to achieve individualized BP control while maximizing long-term kidney and cardiovascular protection.

REFERENCES

1. Kim NH, Seo MH, Jung JH, Han KD, Kim MK, Kim NH. 2023 diabetic kidney disease fact sheet in Korea. *Diabetes Metab J* 2024;48:463-472. PUBMED | CROSSREF
2. de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Diabetes Care* 2022;45:3075-3090. PUBMED | CROSSREF
3. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int* 2022;102 5S:S1-S127. PUBMED | CROSSREF
4. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;375:323-334. PUBMED | CROSSREF
5. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;383:1436-1446. PUBMED | CROSSREF
6. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020;383:2219-2229. PUBMED | CROSSREF
7. Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med* 2021;385:2252-2263. PUBMED | CROSSREF
8. Perkovic V, Tuttle KR, Rossing P, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *N Engl J Med* 2024;391:109-121. PUBMED | CROSSREF
9. Mann JFE, Ørsted DD, Brown-Frandsen K, et al. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med* 2017;377:839-848. PUBMED | CROSSREF
10. Gerstein HC, Colhoun HM, Dagenais GR, et al.; REWIND Investigators. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. *Lancet* 2019;394:131-138. PUBMED | CROSSREF
11. Noh HM, Min SH, Lee HS, Kim SG, Kang JG, Kim JK. Frailty-related factors and 1-year renal function change after sodium-glucose cotransporter-2 inhibitors in elderly chronic kidney disease patients. *Kidney Res Clin Pract* 2025; CROSSREF
12. Wharton S, Calanna S, Davies M, et al. Gastrointestinal tolerability of once-weekly semaglutide 2.4 mg in adults with overweight or obesity, and the relationship between gastrointestinal adverse events and weight loss. *Diabetes Obes Metab* 2022;24:94-105. PUBMED | CROSSREF
13. Agarwal R, Joseph A, Anker SD, et al. Hyperkalemia risk with finerenone: results from the FIDELIO-DKD trial. *J Am Soc Nephrol* 2022;33:225-237. PUBMED | CROSSREF
14. Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;373:2103-2116. PUBMED | CROSSREF
15. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575-1585. PUBMED | CROSSREF
16. Liu J, Li Y, Ge J, et al. Lowering systolic blood pressure to less than 120 mm Hg versus less than 140 mm Hg in patients with high cardiovascular risk with and without diabetes or previous stroke: an open-label, blinded-outcome, randomised trial. *Lancet* 2024;404:245-255. PUBMED | CROSSREF
17. Bi Y, Li M, Liu Y, et al. Intensive blood-pressure control in patients with type 2 diabetes. *N Engl J Med* 2025;392:1155-1167. PUBMED | CROSSREF
18. Beddhu S, Greene T, Boucher R, et al. Intensive systolic blood pressure control and incident chronic kidney disease in people with and without diabetes mellitus: secondary analyses of two randomised controlled trials. *Lancet Diabetes Endocrinol* 2018;6:555-563. PUBMED | CROSSREF

https://doi.org/10.5049/EBP.2026.24.e6

19. Guo X, Sun G, Xu Y, et al. Benefit-harm trade-offs of intensive blood pressure control versus standard blood pressure control on cardiovascular and renal outcomes: an individual participant data analysis of randomised controlled trials. *Lancet* 2025;406:1009-1019. PUBMED | CROSSREF

20. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int* 2021;99 3S:S1-S87. PUBMED | CROSSREF

21. Stergiou GS, Bliziotis IA. Home blood pressure monitoring in the diagnosis and treatment of hypertension: a systematic review. *Am J Hypertens* 2011;24:123-134. PUBMED | CROSSREF

22. Ohkubo T, Kikuya M, Metoki H, et al. Prognosis of "masked" hypertension and "white-coat" hypertension detected by 24-h ambulatory blood pressure monitoring 10-year follow-up from the Ohasama study. *J Am Coll Cardiol* 2005;46:508-515. PUBMED | CROSSREF

23. Kim HL, Lee EM, Ahn SY, et al. The 2022 focused update of the 2018 Korean Hypertension Society Guidelines for the management of hypertension. *Clin Hypertens* 2023;29:11. PUBMED | CROSSREF

24. Jones DW, Ferdinand KC, Taler SJ, et al. 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2025;86:1567-1678. PUBMED | CROSSREF

25. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861-869. PUBMED | CROSSREF

26. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993;329:1456-1462. PUBMED | CROSSREF

27. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851-860. PUBMED | CROSSREF

28. Wang N, Salam A, Pant R, et al. Blood pressure-lowering efficacy of antihypertensive drugs and their combinations: a systematic review and meta-analysis of randomised, double-blind, placebo-controlled trials. *Lancet* 2025;406:915-925. PUBMED | CROSSREF

29. Burnier M, Lin S, Ruilope L, Bader G, Durg S, Brunel P. Effect of angiotensin receptor blockers on blood pressure and renal function in patients with concomitant hypertension and chronic kidney disease: a systematic review and meta-analysis. *Blood Press* 2019;28:358-374. PUBMED | CROSSREF

30. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008;359:2417-2428. PUBMED | CROSSREF

31. Bakris GL, Sarafidis PA, Weir MR, et al. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial. *Lancet* 2010;375:1173-1181. PUBMED | CROSSREF

32. Faucon AL, Fu EL, Stengel B, Mazhar F, Evans M, Carrero JJ. A nationwide cohort study comparing the effectiveness of diuretics and calcium channel blockers on top of renin-angiotensin system inhibitors on chronic kidney disease progression and mortality. *Kidney Int* 2023;104:542-551. PUBMED | CROSSREF

33. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013;369:1892-1903. PUBMED | CROSSREF

34. ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358:1547-1559. PUBMED | CROSSREF

35. The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. *N Engl J Med* 2023;388:117-127. PUBMED | CROSSREF

36. Neuen BL, Fletcher RA, Anker SD, et al. SGLT2 inhibitors and kidney outcomes by glomerular filtration rate and albuminuria: a meta-analysis. *JAMA* 2026;335:233-244. PUBMED | CROSSREF

37. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2024;105 4S:S117-S314. PUBMED | CROSSREF

38. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med* 2013;159:262-274. PUBMED | CROSSREF

39. Baker WL, Buckley LF, Kelly MS, et al. Effects of sodium-glucose cotransporter 2 inhibitors on 24-hour ambulatory blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc* 2017;6:e005686. PUBMED | CROSSREF

40. Kario K, Ferdinand KC, O'Keefe JH. Control of 24-hour blood pressure with SGLT2 inhibitors to prevent cardiovascular disease. *Prog Cardiovasc Dis* 2020;63:249-262. PUBMED | CROSSREF

41. Ferdinand KC, Izzo JL, Lee J, et al. Antihyperglycemic and blood pressure effects of empagliflozin in black patients with type 2 diabetes mellitus and hypertension. *Circulation* 2019;139:2098-2109. PUBMED | CROSSREF

42. Kario K, Okada K, Kato M, et al. Twenty-four-hour blood pressure-lowering effect of a sodium-glucose cotransporter 2 inhibitor in patients with diabetes and uncontrolled nocturnal hypertension: results from the randomized, placebo-controlled SACRA study. *Circulation* 2019;139:2089-2097. PUBMED | CROSSREF

43. Cheng L, Fu Q, Zhou L, et al. Effect of SGLT-2 inhibitor, empagliflozin, on blood pressure reduction in Chinese elderly hypertension patients with type 2 diabetes and its possible mechanisms. *Sci Rep* 2022;12:3525. PUBMED | CROSSREF

44. Nong K, Jeppesen BT, Shi Q, et al. Medications for adults with type 2 diabetes: a living systematic review and network meta-analysis. *BMJ* 2025;390:e083039. PUBMED | CROSSREF

45. Rådholm K, Wu JH, Wong MG, et al. Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular disease, death and safety outcomes in type 2 diabetes - a systematic review. *Diabetes Res Clin Pract* 2018;140:118-128. PUBMED | CROSSREF

46. Zhang S, Qi Z, Wang Y, Song D, Zhu D. Effect of sodium-glucose transporter 2 inhibitors on sarcopenia in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)* 2023;14:1203666. PUBMED | CROSSREF

47. Agarwal R, Filippatos G, Pitt B, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *Eur Heart J* 2022;43:474-484. PUBMED | CROSSREF

48. Agarwal R, Pitt B, Palmer BF, et al. A comparative post hoc analysis of finerenone and spironolactone in resistant hypertension in moderate-to-advanced chronic kidney disease. *Clin Kidney J* 2022;16:293-302. PUBMED | CROSSREF

49. Ruilope LM, Agarwal R, Anker SD, et al. Blood pressure and cardiorenal outcomes with finerenone in chronic kidney disease in type 2 diabetes. *Hypertension* 2022;79:2685-2695. PUBMED | CROSSREF

50. Agarwal R, Green JB, Heerspink HJL, et al. Finerenone with empagliflozin in chronic kidney disease and type 2 diabetes. *N Engl J Med* 2025;393:533-543. PUBMED | CROSSREF

51. Heerspink HJL, Friedman AN, Bjornstad P, et al. Kidney parameters with tirzepatide in obesity with or without type 2 diabetes. *J Am Soc Nephrol* 2025;36:2190-2200. PUBMED | CROSSREF

52. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol* 2019;7:776-785. PUBMED | CROSSREF

53. Kennedy C, Hayes P, Cicero AFG, et al. Semaglutide and blood pressure: an individual patient data meta-analysis. *Eur Heart J* 2024;45:4124-4134. PUBMED | CROSSREF

54. Lingvay I, Mosenzon O, Brown K, et al. Systolic blood pressure reduction with tirzepatide in patients with type 2 diabetes: insights from SURPASS clinical program. *Cardiovasc Diabetol* 2023;22:66. PUBMED | CROSSREF

55. Ribeiro-Silva JC, Tavares CAM, Girardi ACC. The blood pressure lowering effects of glucagon-like peptide-1 receptor agonists: a mini-review of the potential mechanisms. *Curr Opin Pharmacol* 2023;69:102355. PUBMED | CROSSREF

56. Simms-Williams N, Treves N, Yin H, et al. Effect of combination treatment with glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors on incidence of cardiovascular and serious renal events: population based cohort study. *BMJ* 2024;385:e078242. PUBMED | CROSSREF

57. Gourdy P, Darmon P, Dievart F, Halimi JM, Guerci B. Combining glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) in patients with type 2 diabetes mellitus (T2DM). *Cardiovasc Diabetol* 2023;22:79. PUBMED | CROSSREF

58. Mantsiou C, Karagiannis T, Kakotrichi P, et al. Glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors as combination therapy for type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* 2020;22:1857-1868. PUBMED | CROSSREF

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Review Article

Glomerulo–Tubular Crosstalk in Diabetic Kidney Disease: From Pathophysiology to Novel Therapeutics

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ABSTRACT

Diabetic kidney disease (DKD) remains the leading cause of chronic kidney disease and kidney failure worldwide despite advances in glycemic and blood pressure control. Although DKD has traditionally been viewed as a primarily glomerular disorder, growing evidence suggests that its progression is shaped by complex communication between the glomerulus and the tubulointerstitium. Under diabetic conditions characterized by persistent hyperglycemia, oxidative stress, and metabolic imbalance, signaling networks among glomerular endothelial cells, podocytes, and mesangial cells become disrupted. Glomerular injury may generate downstream signals, including proteinuria and loss of protective mediators, that impose inflammatory and metabolic stress on proximal tubular epithelial cells and may activate profibrotic pathways. Conversely, injured tubular cells release cytokines, chemokines, and extracellular vesicles that may influence glomerular cells and further contribute to structural damage. In addition, metabolic disturbances within tubular cells, such as lipid accumulation, mitochondrial dysfunction, and cellular stress responses, may promote tubulointerstitial fibrosis. Viewing DKD as a disorder of disrupted glomerulo–tubular communication provides an integrated framework linking pathophysiological mechanisms with emerging therapeutic strategies aimed at slowing disease progression.

Keywords: Cell communication; Diabetic nephropathies; Fibrosis; Kidney glomerulus; Kidney tubules

INTRODUCTION

Diabetic kidney disease (DKD) is a common and serious microvascular complication of diabetes mellitus, affecting approximately 30–40% of individuals with diabetes worldwide [1]. According to the 2025 edition of the International Diabetes Federation Diabetes Atlas, an estimated 589 million adults were living with diabetes in 2024, and this number is projected to rise further in the coming decades [2]. DKD remains the leading cause of chronic kidney disease (CKD) and new-onset end-stage kidney disease (ESKD) worldwide and significantly increases cardiovascular morbidity and premature mortality [3,4].

Clinically, DKD is characterized by persistent proteinuria, progressive decline in estimated glomerular filtration rate (GFR), and frequently elevated blood pressure [5]. Current standard therapies—including glycemic control, blood pressure management, renin–angiotensin system (RAS) blockade, and sodium–glucose cotransporter 2 (SGLT2) inhibitors—have improved renal outcomes [5]. Nevertheless, many patients continue to experience progressive renal function decline, highlighting the need for a more comprehensive understanding of disease mechanisms [5].

Traditionally, the pathogenesis of DKD has been described primarily from a glomerular perspective, with emphasis on glomerular basement membrane (GBM) thickening, mesangial expansion, and podocyte injury [6]. However, accumulating evidence indicates that tubular injury, particularly involving proximal tubular epithelial cells (PTECs), plays a critical role and may occur early in the disease process [6].

The kidney functions as an integrated organ in which multiple interdependent cell types maintain tissue homeostasis [7]. Communication between the glomerular and tubulointerstitial compartments maintains renal homeostasis but becomes dysregulated under diabetic conditions characterized by hyperglycemia, oxidative stress, and metabolic imbalance [7]. Injury in one compartment can influence others via paracrine mediators, including reactive oxygen species (ROS), inflammatory cytokines, chemokines, and extracellular vesicles (EVs) [7]. Glomerular injury can transmit downstream signals—most notably proteinuria—that stress tubular epithelial cells (TECs), whereas injured tubules may release mediators that affect podocytes and glomerular endothelial integrity, potentially further impairing the glomerular filtration barrier (GFB) [7]. These bidirectional interactions suggest that DKD progression involves coordinated dysfunction across renal compartments rather than isolated injury to individual cell types [7].

This review summarizes the structural and molecular basis of glomerulo–tubular crosstalk in DKD, highlighting descending and ascending signaling pathways and their potential therapeutic implications.

INTRAGLOMERULAR CROSSTALK SIGNALING AXES

The GFB, consisting of glomerular endothelial cells (GECs), the GBM, and podocyte slit diaphragms, is a highly selective filtration interface. Its integrity is maintained by coordinated crosstalk among podocytes, endothelial cells, and mesangial cells (MCs) [8]. In the diabetic milieu, however, hyperglycemia, oxidative stress, and hypoxia render these signaling pathways maladaptive, promoting endothelial dysfunction, podocyte loss, and mesangial expansion [8]. Recent single-cell and biomimetic studies have further defined the key molecular axes involved in this pathogenic crosstalk [8], which are summarized in **Fig. 1A**.

Vascular endothelial growth factor A (VEGF-A)/VEGF receptor (VEGFR) signaling axis

VEGF-A is a key mediator of podocyte-to-GEC crosstalk. Podocyte-derived VEGF-A binds VEGFR-2 on adjacent GECs and is essential for maintaining endothelial fenestrations and GEC survival [9]. In early DKD, high glucose may enhance VEGF-A/VEGFR-2 signaling, contributing to abnormal angiogenesis, endothelial injury, and hyperpermeability, whereas in advanced DKD, loss of podocyte-derived VEGF-A promotes endothelial apoptosis,

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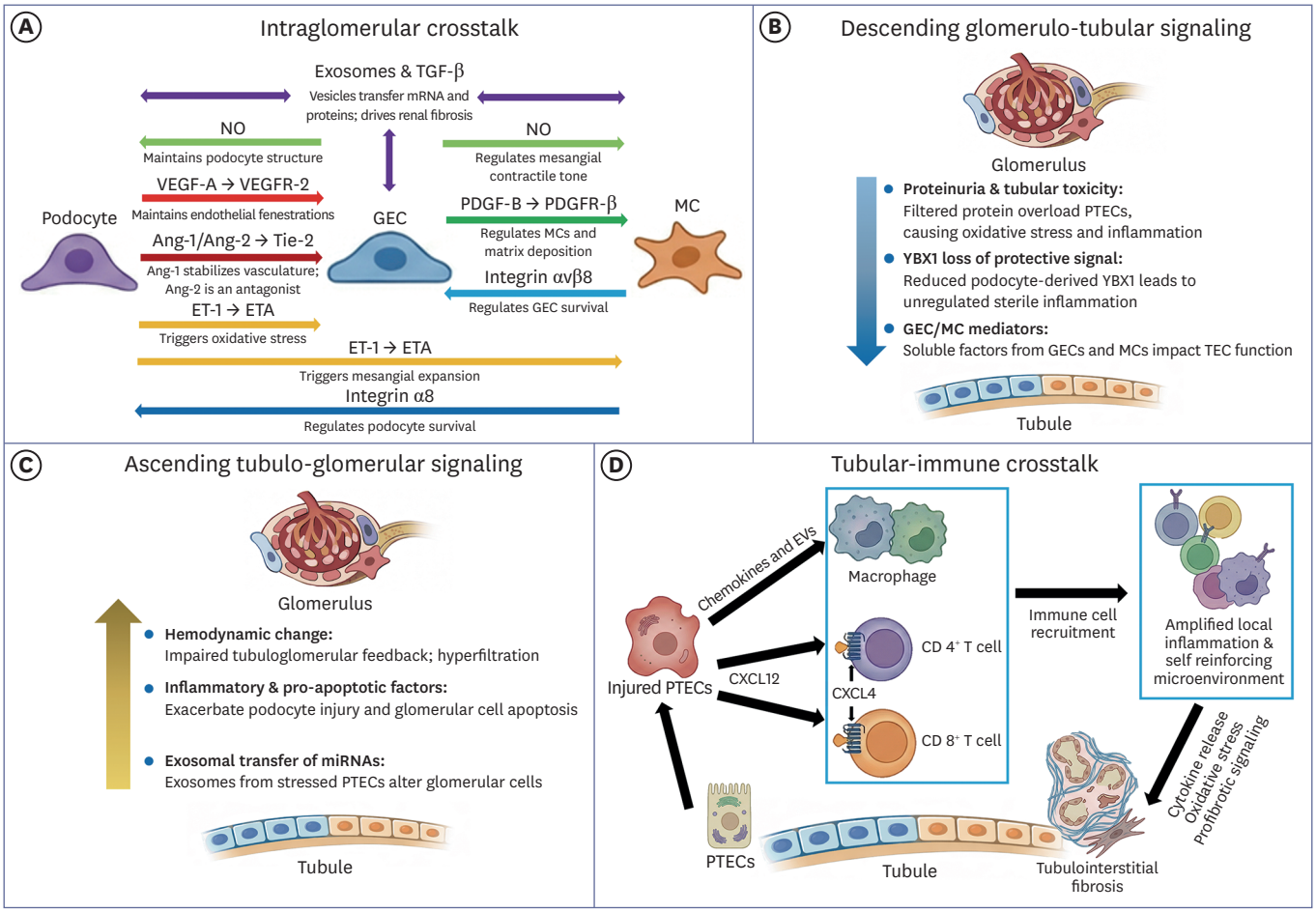

Fig. 1. Integrated glomerulo–tubular–immune crosstalk in DKD. (A) Intraglomerular crosstalk among podocytes, GECs, and MCs, including major signaling pathways such as VEGF-A, ET-1, PDGF-B, nitric oxide, integrin-mediated interactions, and extracellular vesicle-associated signaling. (B) Descending glomerulo–tubular signaling, whereby glomerular injury transmits pathogenic signals to PTECs, including proteinuria-induced tubular toxicity, loss of podocyte-derived YBX1, and soluble mediators from GECs/MCs. (C) Ascending tubulo–glomerular signaling, whereby injured tubular cells modulate glomerular structure and function through altered tubuloglomerular feedback, IL-6/Rab5 signaling, Sirt1/NMN/Claudin-1-related pathways, and exosomal transfer. (D) Tubular–immune crosstalk, in which stressed tubular cells recruit and activate immune cells through chemokines such as CXCL12, thereby amplifying inflammation and tubulointerstitial fibrosis.
Ang-1/Ang-2, angiopoietin-1/angiopoietin-2; CXCL12, C-X-C motif chemokine ligand 12; DKD, diabetic kidney disease; ET-1, endothelin-1; ETA, endothelin receptor type A; EV, extracellular vesicle; GEC, glomerular endothelial cell; IL-6, interleukin-6; integrin α8, integrin alpha 8; integrin αvβ8, integrin alpha V beta 8; MC, mesangial cell; NMN, nicotinamide mononucleotide; NO, nitric oxide; PDGF-B, platelet-derived growth factor B; PDGFR-β, platelet-derived growth factor receptor beta; PTEC, proximal tubular epithelial cell; Rab5, Ras-related protein Rab-5A; Sirt1, sirtuin 1; TGF-β, transforming growth factor beta; Tie-2, tyrosine kinase with immunoglobulin-like and epidermal growth factor-like domains 2; VEGF-A, vascular endothelial growth factor A; VEGFR-2, vascular endothelial growth factor receptor 2; YBX1, Y-box binding protein 1.

capillary collapse, and glomerulosclerosis [9]. Semaphorin 3A further modulates this axis by competing for Neuropilin-1 and inhibiting VEGF-A signaling [9].

Angiopoietin (Ang)/tyrosine kinase with immunoglobulin-like and epidermal growth factor-like domains 2 (Tie-2) system

The Ang–Tie signaling pathway is another pivotal regulator of vascular stability and endothelial permeability [10]. Podocytes constitutively secrete Ang-1, which binds to the Tie-2 receptor tyrosine kinase expressed on GECs to promote endothelial survival and stabilize the microvasculature [11]. In contrast, Ang-2 is synthesized primarily by GECs and acts as a competitive antagonist of Ang-1 at the Tie-2 receptor [11]. In DKD, Ang-1 expression decreases while Ang-2 is significantly upregulated, leading to a diminished Ang-1/Ang-2 ratio [10].

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This imbalance impairs Tie-2 phosphorylation, sensitizes endothelial cells to pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), and accelerates GEC apoptosis and proteinuria [10]. Additionally, elevated Ang-2 under high-glucose conditions also induces MC apoptosis, indicating its broader role in intraglomerular damage [12].

Endothelin-1 (ET-1)/endothelin receptor type A (ETA) axis

ET-1 is a potent vasoconstrictor that mediates pathological podocyte–endothelial crosstalk. Under diabetic conditions, mechanical stress and transforming growth factor-beta (TGF-β) activation stimulate podocytes to secrete excessive ET-1 [13]. This podocyte-derived ET-1 binds in a paracrine manner to ETA expressed on GECs. Activation of this axis induces marked mitochondrial oxidative stress in GECs, leading to endothelial dysfunction and degradation of the endothelial surface layer (glycocalyx) [13]. The ET-1/ETA axis may also contribute to mesangial expansion. GEC-derived ET-1 acts on ETA expressed on MCs, thereby accelerating extracellular matrix accumulation and mesangial proliferation through activation of the RhoA/Rho-associated protein kinase (ROCK) pathway [14].

Platelet-derived growth factor-B (PDGF-B)/platelet-derived growth factor receptor-beta (PDGFR-β) axis

Communication between GECs and MCs is predominantly orchestrated by the PDGF system. GECs synthesize and secrete PDGF-B, while its specific receptor, PDGFR-β, is localized almost exclusively on MCs [15]. In a healthy kidney, this axis is responsible for recruiting MCs to the developing capillary tuft to provide structural support [15]. In the diabetic milieu, dysregulated activation of the PDGF-B/PDGFR-β pathway may hyperactivate MCs, thereby contributing to pathological mesangial proliferation, extracellular matrix accumulation, and mesangial expansion, which are hallmarks of diabetic glomerular injury [15].

Nitric oxide (NO) and gasotransmitter signaling

Endothelial nitric oxide synthase (eNOS) expressed in GECs produces NO, a critical gasotransmitter that diffuses to adjacent podocytes and MCs [16]. Endothelium-derived NO is essential for maintaining podocyte cytoskeletal structure and function; deficiency of eNOS greatly exacerbates podocyte injury, proteinuria, and glomerulosclerosis in DKD [16]. Concurrently, NO regulates the contractile tone of MCs, modulating intraglomerular capillary blood flow [17]. In diabetes, while eNOS protein expression may initially increase, the bioavailability of NO is sharply reduced due to eNOS uncoupling and quenching of NO by excessive superoxide radicals, leading to severe endothelial and podocyte dysfunction [18].

Exosome-mediated crosstalk and TGF-β signaling

Beyond traditional soluble ligands, intraglomerular cells utilize EVs, such as exosomes, to transfer mRNA, microRNAs (miRNAs), and proteins [19,20]. TGF-β acts as a core driver of renal fibrosis and interacts intricately with these vesicles [19]. For instance, GECs exposed to high glucose secrete exosomes enriched in TGF-β1 mRNA and circular RNAs [19]. Upon uptake by MCs, these exosomes activate the TGF-β1/Smad and phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathways, instigating mesangial activation, proliferation, and robust extracellular matrix overproduction [19]. GEC-derived exosomes also target podocytes, where TGF-β1 activates the Wnt/β-catenin pathway, inducing epithelial–mesenchymal transition (EMT) and podocyte dedifferentiation [21]. Conversely, stressed MCs release exosomes that upregulate TGF-β1 receptors in podocytes, facilitating podocyte apoptosis and detachment [22].

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Integrin-mediated interactions

Integrins facilitate direct cell–matrix and cell–cell adhesion and act as bidirectional mechanotransducers [23]. MCs express integrin alpha V beta 8 (integrin αvβ8), which acts as a protective mediator for GECs. Integrin αvβ8 tightly sequesters latent TGF-β in the mesangium; loss or reduction of this integrin under diabetic conditions releases bioactive TGF-β, which subsequently provokes GEC apoptosis and exacerbates microvascular damage [23]. Similarly, MCs express integrin α8, which provides critical structural and survival signals to podocytes; experimental deletion of integrin alpha 8 (integrin α8) in diabetic models results in accelerated podocyte loss and severe glomerulosclerosis [24].

GLOMERULO–TUBULAR CROSSTALK: DESCENDING SIGNAL

Historically, structural deterioration of the glomerulus was considered the primary and isolated driver of DKD. However, contemporary research has established that injury initiated within the GFB inevitably transmits pathological "descending" signals to the downstream tubulointerstitial compartment (**Fig. 1B**) [7]. This unidirectional glomerulo–tubular crosstalk is a critical determinant of renal functional decline and operates through both classical mechanical overload of the filtrate and dysregulation of specific paracrine signaling molecules [7].

Proteinuria-induced tubular toxicity

The best-characterized descending signal linking glomerular injury to tubular damage in DKD is proteinuria, which acts as a major toxic stressor to tubular cells [25]. Under healthy conditions, the GFB restricts the passage of large macromolecules. However, as the diabetic milieu compromises podocyte and GEC integrity, massive quantities of serum albumin and other proteins leak into the ultrafiltrate. PTECs attempt to compensate by indiscriminately reabsorbing these filtered proteins, rapidly leading to cellular overload [25].

Excessive protein uptake induces oxidative stress, activates the RAS, and promotes advanced glycation end products accumulation in PTECs [25,26]. Albumin overload also activates Wnt/β-catenin signaling and the Toll-like receptor 4 (TLR4)/NOD-like receptor family pyrin domain–containing 3 (NLRP3) inflammasome axis, leading to inflammatory cytokine release and structural injury [27,28]. Sustained proteinuric stress may drive EMT-like changes, hypertrophy, detachment, and apoptosis in PTECs, thereby promoting tubulointerstitial fibrosis and progression to ESKD [25,26].

Loss of protective podocyte-derived Y-box binding protein 1 (YBX1)

YBX1 is a key mediator of protective glomerulo-tubular crosstalk. Under physiological conditions, podocytes secrete YBX1 into the urinary space [29]. YBX1 binds TLR4 on the apical surface of tubular cells and inhibits TLR4 signaling [29]. This suppresses nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) phosphorylation and NLRP3 inflammasome activation in PTECs [29]. Loss of this protective signal may promote tubular inflammation and accelerate DKD progression [29].

In DKD pathogenesis, podocyte injury and depletion lead to a significant reduction in YBX1 secretion. Loss of this inhibitory descending signal may permit dysregulated TLR4 signaling in the tubular compartment [29]. Consequently, the tubular compartment may

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develop sterile inflammation characterized by increased kidney injury molecule-1 expression, macrophage infiltration, and progressive tubulointerstitial fibrosis [29]. Disruption of this YBX1-mediated glomerulo–tubular crosstalk highlights how loss of a protective descending signal can be as detrimental as the presence of a toxic one.

GEC and MC mediators

In addition to podocytes, other resident glomerular cells actively participate in descending communication [30]. GECs interact with TECs by secreting specific soluble factors into the filtrate [30]. For example, GECs secrete hepatocyte growth factor and various insulin-like growth factor-binding proteins [30]. These mediators travel downstream and bind to receptors on PTECs, where they may either protect or injure the tubular epithelium depending on disease stage [30].

TUBULO–GLOMERULAR CROSSTALK: ASCENDING SIGNAL

Historically, DKD pathogenesis was predominantly viewed through a "top-down," descending perspective, where glomerular injury trickled down to damage the tubules [7]. However, contemporary evidence highlights that PTECs are not merely passive victims; they actively engage in retrograde, or "ascending," crosstalk with the glomerular compartment (**Fig. 1C**) [7]. This tubulo-glomerular communication influences glomerular hemodynamics, structural integrity, and DKD progression through several pathways [7].

Hemodynamic regulation via tubuloglomerular feedback

One of the best-characterized ascending mechanisms is tubuloglomerular feedback, which regulates renal microcirculation and single-nephron GFR [31]. The macula densa, composed of specialized TECs, senses sodium chloride concentrations in the distal filtrate [31]. In the diabetic kidney, upregulation of SGLT2 in the proximal tubules leads to excessive, coupled reabsorption of glucose and sodium [32]. Consequently, sodium delivery to the macula densa is drastically reduced [32]. This altered sensing blunts tubuloglomerular feedback, promotes release of vasoactive mediators via NO and adenosine pathways, dilates the afferent arteriole, and exacerbates glomerular hyperfiltration [32].

TEC-to-podocyte crosstalk: inflammatory and apoptotic signals

Injured tubules release mediators that can impair podocyte structure and function.

- Interleukin (IL)-6/Ras-related protein Rab-5A (Rab5) axis: Under hyperglycemic and proteinuric stress, PTECs secrete elevated levels of IL-6, which acts directly on podocytes to upregulate Rab5, a small GTPase [33]. This activation triggers pathological endocytosis and internalization of nephrin from the podocyte surface, leading to slit-diaphragm disruption, cytoskeletal dysmorphology, and functional failure [33].
- Bcl-2–interacting mediator of cell death (Bim)/nuclear factor of activated T cells 2 (NFAT2) pathway: High-glucose conditions upregulate the expression of the pro-apoptotic protein Bim in PTECs [34]. Tubular Bim expression subsequently transmits signals to podocytes, triggering F-actin cytoskeletal rearrangement, downregulation of synaptophysin, and apoptosis via the downstream NFAT2/Bax signaling pathway [34].
- Sirtuin 1 (Sirt1)/nicotinamide mononucleotide (NMN)/Claudin-1 axis: Healthy PTECs exert a protective effect on podocytes through Sirt1 and the NMN axis [35]. Tubular Sirt1 physiologically suppresses abnormal overexpression of the tight-junction protein Claudin-1 in podocytes and parietal epithelial cells via NMN-mediated crosstalk [35].

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In DKD, decline of tubular Sirt1 relieves this inhibition, leading to slit-diaphragm destabilization and severe podocyte injury [35].

- Gremlin: Tubular-derived factors, such as the bone morphogenetic protein antagonist Gremlin, have also been shown to promote podocyte loss, foot process effacement, and severe tubulointerstitial damage when overexpressed in the tubules [36].

TEC-to-GEC crosstalk

The tubulointerstitium regulates the health of the glomerular endothelium through secretion of angiogenic factors [30]. Under physiological conditions, TECs produce VEGF-A and Ang-1, which bind to VEGFR and Tie-2 receptors on GECs to maintain endothelial fenestrations and microvascular stability [30]. During early DKD, TECs may transiently upregulate these factors to stimulate neovascularization [30]; however, as severe tubular injury develops in late-stage DKD, production of VEGF-A and Ang-1 sharply declines [30,37]. This deprivation of vital survival signals accelerates endothelial apoptosis, capillary collapse, and structural damage [37]. Additionally, hypoxic and inflamed TECs secrete high mobility group box 1 and upregulate hypoxia-inducible factor 1-alpha, thereby driving the release of pro-inflammatory cytokines, including TNF-α and IL-1β as well as ROS, which induce endothelial-to-mesenchymal transition and widespread GEC dysfunction [38].

TEC-to-MC crosstalk via EVs

In addition to soluble cytokines and growth factors, TECs utilize EVs, particularly exosomes, to conduct precise ascending communication with MCs. Under high-glucose conditions, stressed PTECs secrete exosomes enriched with specific miRNAs, notably miR-92a-1-5p [39]. These tubular-derived exosomes travel retrogradely and are internalized by MCs within the glomerulus [39]. Upon uptake, miR-92a-1-5p has been shown to induce significant endoplasmic reticulum stress and may trigger myofibroblast transdifferentiation in the mesangial compartment [39]. This exosome-mediated TEC-to-MC crosstalk may promote mesangial activation, proliferation, and extracellular matrix overproduction, thereby driving diabetic glomerulosclerosis [39].

TUBULO–IMMUNE CROSSTALK

Recent studies have highlighted the importance of immune-mediated mechanisms in the progression of DKD. Injured PTECs actively interact with immune cells by releasing chemokines and inflammatory mediators that may recruit immune populations into the tubulointerstitium [40]. Among these mediators, C-X-C motif chemokine ligand 12 (CXCL12) has emerged as a key regulator of tubular–immune communication, as illustrated in **Fig. 1D** [40].

Single-cell transcriptomic analyses have shown that stressed PTECs exhibit increased expression of CXCL12, which binds to its receptor C-X-C motif chemokine receptor 4 (CXCR4) expressed on T cells [40]. This signaling axis may promote recruitment of $CD4^+$ and $CD8^+$ effector T cells into the renal interstitium, thereby amplifying local inflammation [40]. The accumulation of activated immune cells further enhances cytokine release, oxidative stress, and profibrotic signaling pathways, thereby accelerating tubulointerstitial fibrosis [40].

In addition to T cell recruitment, tubular cells may interact with macrophages and other immune populations through chemokines and EVs. These immune–tubular interactions may

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establish a self-reinforcing inflammatory microenvironment that contributes to progressive renal injury in DKD [40].

NOVEL THERAPEUTIC PERSPECTIVES

DKD can be understood as a disease of disrupted glomerulo–tubular crosstalk, a perspective that helps explain disease progression and guides the development of targeted therapies. Accordingly, this section classifies current and emerging treatments by the intercellular communication axis they primarily affect and by level of evidence: Level 1, clinically established therapies supported by randomized controlled trials; Level 2, agents under active clinical investigation; and Level 3, preclinical candidates (**Table 1**).

Targeting intraglomerular crosstalk

● **Level 1: Clinically established**

ET receptor antagonism: atrasentan

The ET-1/ETA axis mediates pathological podocyte-to-GEC and GEC-to-MC crosstalk. Atrasentan selectively antagonizes ETA, thereby blocking ET-1–driven mitochondrial oxidative stress in GECs and RhoA/ROCK-dependent mesangial matrix accumulation [41]. In the

Table 1. Summary of crosstalk-targeted therapeutics in DKD, stratified by evidence level

Evidence level	Agent	Crosstalk target	Mechanism on crosstalk	Key clinical evidence
Level 1 Clinical	SGLT2 inhibitors (empagliflozin, dapagliflozin)	Ascending: tubuloglomerular feedback, hemodynamic; Descending: NLRP3 inflammasome	Restores tubuloglomerular feedback; reduces NLRP3/AMPK-Sirt1/PGC-1α; protects podocyte autophagy	CREDENCE; DAPA-CKD; EMPA-KIDNEY
Level 1 Clinical	GLP-1 receptor agonists (semaglutide, liraglutide)	Descending: eNOS/endothelial; Tubulo–immune: NF-κB	Restores eNOS activity; attenuates NF-κB-linked tubular inflammation	FLOW trial (semaglutide); CREDENCE sub-analyses
Level 1 Clinical	Non-steroidal MRA (finerenone)	Descending: RXRα/MR-lipid; Ascending: PI3K/Akt/eNOS	Suppresses tubular senescence via RXRα/MR inhibition; PI3K/Akt/eNOS in GECs	FIDELIO-DKD; FIGARO-DKD
Level 1 Clinical	Endothelin receptor antagonist (atrasentan)	Intraglomerular: ET-1/ETA; Descending: TGF-β/Smad	Blocks ET-1→ETA on GEC/MC; suppresses ER-stress apoptosis and TGF-β/Smad fibrosis	SONAR trial (Phase 3)
Level 1 Clinical	DPP-4 inhibitor (linagliptin)	Descending: soluble DPP-4/TGF-β autocrine loop	Prevents sDPP-4-induced TGFβR activation in PTECs; suppresses EMT/fibrogenesis	MARLINA-T2D; mechanistic RCTs
Level 2 Clinical trial	NMN supplementation	Ascending: IL-6/Rab5→nephrin endocytosis; Sirt1/NMN/Claudin-1	Restores Sirt1; downregulates Rab5; blocks nephrin internalization; suppresses Claudin-1	Phase I/II (NCT trials ongoing); preclinical DKD models
Level 2 Clinical trial	IL-6 neutralizing antibodies (tocilizumab, others)	Ascending: IL-6/Rab5 axis (TEC→podocyte)	Prevents IL-6-driven Rab5 activation; preserves slit-diaphragm integrity	Phase II exploratory in CKD; DKD-specific trials pending
Level 2 Clinical trial	Anti-CXCL12 neutralizing Ab	Tubulo–immune: CXCL12/CXCR4 T-cell recruitment	Blocks chemotactic gradient; reduces $CD4^+$/$CD8^+$ TEM infiltration; attenuates interstitial fibrosis	Preclinical proof-of-concept; CXCR4 antagonist (plerixafor) in Phase II trials
Level 3 Preclinical	Celastrol	Descending: miR-192-5p/miR-21-5p/TGF-β1; Ascending: Nrf2/autophagy	Suppresses miR-192-5p/miR-21-5p→TGF-β1/MMP-2; restores LC3/Beclin-1 autophagy; activates Nrf2	In vitro & diabetic rodent models only
Level 3 Preclinical	MSC-derived small EVs (miR-23a-3p)	Descending/Ascending: KLF3/STAT3 in PTECs; mitochondrial transfer	miR-23a-3p inhibits KLF3/STAT3 fibrotic axis; MSC mitochondria rescue tubular bioenergetics	Streptozotocin mouse models; no human data
Level 3 Preclinical	METTL3 inhibitor/ Smad7 miRNA	Descending: m6A-ZEB2 tubular EMT; TGF-β1/Smad	METTL3 inhibition blocks m6A-ZEB2 translation; nanoparticle-miRNA restores Smad7 brake	Diabetic cell & animal models; delivery platforms in development

Akt, protein kinase B; CKD, chronic kidney disease; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, C-X-C motif chemokine receptor 4; DKD, diabetic kidney disease; DPP-4, dipeptidyl peptidase-4; EMT, epithelial–mesenchymal transition; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; ET-1, endothelin-1; ETA, endothelin receptor type A; EV, extracellular vesicle; GEC, glomerular endothelial cell; GLP-1, glucagon-like peptide-1; IL, interleukin; MC, mesangial cell; MMP-2, matrix metalloproteinase-2; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; MSC, mesenchymal stem cell; NCT, National Clinical Trial; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-like receptor family pyrin domain–containing 3; NMN, nicotinamide mononucleotide; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K, phosphoinositide 3-kinase; PTEC, proximal tubular epithelial cell; Rab5, Ras-related protein Rab-5A; RCT, randomized controlled trial; RXRα, retinoid X receptor alpha; SGLT2, sodium–glucose cotransporter 2; Sirt1, sirtuin 1; TEC, tubular epithelial cell; TEM, transmission electron microscopy; TGF-β, transforming growth factor-beta; ZEB2, zinc finger E-box-binding homeobox 2.

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SONAR Phase 3 trial, atrasentan significantly reduced the risk of renal events in patients with type 2 diabetes and CKD, providing direct clinical validation that intraglomerular ET-1 signaling is a tractable therapeutic target [41].

● **Level 1: Clinically established**

SGLT2 inhibitors: podocyte protection via intraglomerular hemodynamics

SGLT2 inhibitors restore tubuloglomerular feedback, thereby reducing intraglomerular hypertension and mechanical stress [42]. They may also directly protect podocytes by enhancing autophagy, preserving slit diaphragm integrity, and reducing oxidative stress [43]. These intraglomerular benefits are in addition to the canonical tubular actions of this drug class and have been reflected in the sustained albuminuria reduction observed in the CREDENCE and EMPA-KIDNEY trials [42,43].

Targeting descending glomerulo–tubular signals

● **Level 1: Clinically established**

SGLT2 inhibitors: NLRP3 inflammasome suppression and tubular cytoprotection

Beyond restoring TGF-mediated hemodynamics, SGLT2 inhibitors directly attenuate the cellular consequences of proteinuric overload in PTECs. Inhibition of SGLT2 has been shown to suppress NLRP3 inflammasome activation—a central effector of albumin overload–induced tubular injury—and to improve mitochondrial homeostasis through AMPK–Sirt1/peroxisome proliferator-activated receptor gamma coactivator 1-alpha cytoprotective programs [42]. These pleiotropic tubular effects are thought to contribute to the slowing of GFR decline observed beyond what hemodynamic effects alone would predict in the DAPA-CKD and EMPA-KIDNEY trials [42].

● **Level 1: Clinically established**

Non-steroidal mineralocorticoid receptor antagonist: finerenone

Finerenone addresses descending tubular injury through 2 complementary mechanisms. First, it has been reported to suppress cellular senescence and metabolic reprogramming in PTECs by inhibiting the retinoid X receptor alpha/mineralocorticoid receptor pathway, reducing lipid accumulation and interstitial fibrosis [44]. Second, it activates the PI3K/Akt/eNOS pathway in GECs, mitigating oxidative damage and mitochondrial fragmentation—thereby partly restoring the protective endothelium-derived NO signal that physiologically supports podocyte structure [44]. The FIDELIO-DKD and FIGARO-DKD trials established finerenone's kidney-protective efficacy beyond RAS blockade, consistent with these crosstalk-disrupting mechanisms [44].

● **Level 1: Clinically established**

Dipeptidyl peptidase-4 (DPP-4) inhibitors: linagliptin

Soluble DPP-4 secreted by PTECs under diabetic stress activates TGF-β receptor signaling in an autocrine manner, sustaining a self-reinforcing inflammatory and fibrogenic loop within the tubular compartment. Linagliptin may interrupt this descending autocrine crosstalk by preventing soluble DPP-4–mediated TGFβR activation, thereby attenuating EMT and TGF-β1–driven fibrogenesis in PTECs [45]. This mechanistic action complements the glomerular endothelial benefits of improved eNOS activity associated with incretin-based therapies [45].

● **Level 1: Clinically established**

Glucagon-like peptide-1 (GLP-1) receptor agonists: endothelial crosstalk and tubular NF-κB attenuation

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GLP-1 receptor agonists (liraglutide, semaglutide) modulate descending crosstalk at 2 levels. In the glomerulus, they may restore eNOS activity in GECs, partially correcting the NO deficiency that contributes to podocyte cytoskeletal dysfunction [46]. In the tubulointerstitium, they may attenuate NF-κB–linked inflammatory signaling in PTECs, reducing the production of pro-inflammatory cytokines that would otherwise amplify tubular injury and profibrotic remodeling [46]. The FLOW trial demonstrated that semaglutide reduces kidney failure and death from kidney disease in patients with type 2 diabetes and CKD, providing the first dedicated renal outcomes evidence for this class [46].

Targeting ascending tubulo–glomerular signals

● **Level 1: Clinically established**

SGLT2 inhibitors: restoring tubuloglomerular feedback

The most well-characterized ascending mechanism in DKD is impaired tubuloglomerular feedback caused by excessive SGLT2-mediated sodium reabsorption. By promoting urinary sodium excretion, SGLT2 inhibitors restore sodium delivery to the macula densa, normalizing adenosine-mediated afferent arteriolar tone and alleviating glomerular hyperfiltration [32,42]. This crosstalk-restoring action is mechanistically distinct from the tubular cytoprotective effects described above and underscores the multi-site impact of this drug class across both descending and ascending signaling circuits.

● **Level 2: Under clinical investigation**

NMN supplementation: intercepting the IL-6/Rab5 and Sirt1/Claudin-1 axes

Under hyperglycemic stress, PTECs secrete excess IL-6, which acts on podocytes to upregulate Rab5—a GTPase that drives nephrin endocytosis and slit-diaphragm disassembly [33]. Simultaneously, declining tubular Sirt1 releases the inhibitory brake on Claudin-1 overexpression in podocytes via NMN-mediated crosstalk, further destabilizing the filtration barrier [35]. NMN administration addresses both axes simultaneously: by restoring Sirt1 activity, NMN may suppress Rab5 expression and limit nephrin internalization while re-engaging the protective Sirt1-NMN-Claudin-1 circuit [33,35]. Phase I/II clinical investigations of NMN supplementation are ongoing, though DKD-specific randomized trial data are not yet available [33].

● **Level 2: Under clinical investigation**

IL-6 neutralizing antibodies: direct blockade of TEC-to-podocyte crosstalk

IL-6 neutralization (e.g., tocilizumab-class agents) may directly inhibit the ascending IL-6/Rab5 signal from stressed PTECs to podocytes, preserving nephrin surface expression and slit-diaphragm architecture [33]. Exploratory Phase II data in CKD patients suggest anti-inflammatory benefit, but dedicated DKD trials with hard renal endpoints are pending [33]. This axis represents an attractive target given its specificity for the TEC-to-podocyte ascending circuit and the availability of approved anti-IL-6 biologics.

Targeting tubular–immune crosstalk

● **Level 2: Under clinical investigation**

Anti-CXCL12 neutralizing antibodies and CXCR4 antagonists

In experimental DKD models, anti-CXCL12 neutralizing antibodies reduced the accumulation of activated T cell subsets in the renal interstitium, attenuating the local inflammatory milieu and associated fibrotic signaling [40]. The CXCR4 antagonist plerixafor, already approved for hematopoietic stem cell mobilization, has entered Phase II investigation in inflammatory kidney diseases. Translating this strategy to DKD requires establishing the

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relative contribution of CXCL12/CXCR4 signaling to tubulo–immune crosstalk in human disease, which recent single-cell transcriptomic datasets are beginning to address [40].

Multi-axis modulators and advanced regenerative strategies

● **Level 3: Preclinical candidates**

Celastrol: convergent suppression of miRNA-driven descending and ascending fibrosis

Celastrol, a pentacyclic triterpenoid, has been shown to suppress the pathological upregulation of miR-192-5p and miR-21-5p in the diabetic kidney, thereby reducing TGF-β1 and matrix metalloproteinase-2 expression and attenuating tubulointerstitial fibrosis along both descending and ascending crosstalk axes [47]. It additionally restores autophagic flux via LC3/Beclin-1 upregulation, modulates the Bcl-2/caspase-3 apoptotic balance, and activates the Nrf2 antioxidant pathway [47]. To date, evidence is confined to in vitro systems and diabetic rodent models; formulation for human use and formal clinical investigation have not yet commenced [47].

● **Level 3: Preclinical candidates**

Mesenchymal stem cell (MSC)-derived EVs: paracrine rescue of tubular crosstalk

MSC–derived small EVs enriched with miR-23a-3p have been shown to inhibit the KLF3/STAT3 profibrotic axis in PTECs, attenuating the tubular stress that drives both descending inflammation and ascending signals to glomerular cells [48]. MSCs also have been reported to transfer functional mitochondria to metabolically stressed tubular cells, restoring mitochondrial quality control and limiting the bioenergetic failure that amplifies crosstalk-mediated injury [48]. These findings are currently limited to streptozotocin-induced diabetic mouse models; scalable manufacturing and immunogenicity remain key translational barriers [48].

● **Level 3: Preclinical candidates**

Epigenetic and non-coding RNA therapeutics: methyltransferase-like 3 (METTL3) inhibition and Smad7 restoration

High-glucose and inflammatory stress reshape epitranscriptomic regulation in TECs. METTL3-mediated m6A modification may enhance translational efficiency of zinc finger E-box-binding homeobox 2 mRNA, promoting tubular EMT and fibrotic remodeling along the descending signaling axis [49]. Experimental METTL3 inhibition attenuates this process in diabetic models [49]. In parallel, nanoparticle-mediated delivery of exogenous miRNAs targeting the TGF-β1/Smad pathway—by restoring the inhibitory regulator Smad7—has demonstrated efficacy in diabetic kidney injury models [49]. These strategies are currently at the delivery platform development stage, with systemic off-target effects and renal targeting efficiency as central unresolved challenges [49].

Future outlook: precision nephrology targeting crosstalk networks

The stratification of DKD therapeutics by crosstalk circuit and evidence level reveals a structurally coherent but incomplete landscape. Clinically established agents—SGLT2 inhibitors, GLP-1 receptor agonists, finerenone, atrasentan, and linagliptin—exert their kidney-protective effects in part by modulating specific intercellular communication networks, though this mechanistic framing has only recently been articulated. By contrast, the ascending tubulo–glomerular axes (IL-6/Rab5, Sirt1/NMN/Claudin-1, exosomal miR-92a-1-5p) and the tubular–immune CXCL12/CXCR4 circuit currently lack dedicated clinical-stage interventions with hard renal endpoints.

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Next-generation technologies are accelerating the identification of new crosstalk-targeted therapies. Single-cell and spatial transcriptomics can now map ligand–receptor interactions at single-cell resolution within specific renal microenvironments, enabling the discovery of novel crosstalk nodes beyond those currently catalogued [50]. Kidney organoids and microfluidic glomerulus-on-a-chip platforms provide experimentally tractable systems to validate crosstalk-targeted candidates before clinical translation [50]. Integrating these platforms with the evidence-tiered therapeutic framework may help identify and prioritize promising crosstalk-targeted strategies for future translational research and clinical evaluation.

In conclusion, DKD is increasingly recognized as a multicompartmental disorder in which bidirectional communication between the glomerulus and the tubulointerstitium contributes to progressive injury beyond the glomerulus alone. Descending signals from injured glomerular cells, together with ascending inflammatory and metabolic signals from stressed TECs, form interconnected networks that may promote immune activation, structural remodeling, and fibrosis. Framing DKD as a disease of disrupted glomerulo–tubular crosstalk provides a more integrated view of pathogenesis and highlights potential therapeutic opportunities. Beyond conventional therapies, restoring hemodynamic balance and modulating maladaptive intercellular signaling may help slow DKD progression.

REFERENCES

1. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. *Clin J Am Soc Nephrol* 2017;12:2032-2045. PUBMED | CROSSREF
2. Ceriello A, Colagiuri S. IDF global clinical practice recommendations for managing type 2 diabetes - 2025. *Diabetes Res Clin Pract* 2025;222 Suppl 1:112152. PUBMED | CROSSREF
3. Thomas MC, Brownlee M, Susztak K, et al. Diabetic kidney disease. *Nat Rev Dis Primers* 2015;1:15018. PUBMED | CROSSREF
4. Makmun A, Satirapoj B, Tuyen DG, et al. The burden of chronic kidney disease in Asia region: a review of the evidence, current challenges, and future directions. *Kidney Res Clin Pract* 2025;44:411-433. PUBMED | CROSSREF
5. Martinez Leon V, Hilburg R, Susztak K. Mechanisms of diabetic kidney disease and established and emerging treatments. *Nat Rev Endocrinol* 2026;22:21-35. PUBMED | CROSSREF
6. Gilbert RE. Proximal tubulopathy: prime mover and key therapeutic target in diabetic kidney disease. *Diabetes* 2017;66:791-800. PUBMED | CROSSREF
7. Fogo AB, Harris RC. Crosstalk between glomeruli and tubules. *Nat Rev Nephrol* 2025;21:189-199. PUBMED | CROSSREF
8. Hu S, Hang X, Wei Y, Wang H, Zhang L, Zhao L. Crosstalk among podocytes, glomerular endothelial cells and mesangial cells in diabetic kidney disease: an updated review. *Cell Commun Signal* 2024;22:136. PUBMED | CROSSREF
9. Mahtal N, Lenoir O, Tharaux PL. Glomerular endothelial cell crosstalk with podocytes in diabetic kidney disease. *Front Med (Lausanne)* 2021;8:659013. PUBMED | CROSSREF
10. Gnudi L. Angiopoietins and diabetic nephropathy. *Diabetologia* 2016;59:1616-1620. PUBMED | CROSSREF
11. Satchell SC, Harper SJ, Tooke JE, Kerjaschki D, Saleem MA, Mathieson PW. Human podocytes express angiopoietin 1, a potential regulator of glomerular vascular endothelial growth factor. *J Am Soc Nephrol* 2002;13:544-550. PUBMED | CROSSREF
12. Tsai YC, Kuo PL, Hung WW, et al. Angpt2 induces mesangial cell apoptosis through the microRNA-33-5p-SOCS5 loop in diabetic nephropathy. *Mol Ther Nucleic Acids* 2018;13:543-555. PUBMED | CROSSREF
13. Daehn I, Casalena G, Zhang T, et al. Endothelial mitochondrial oxidative stress determines podocyte depletion in segmental glomerulosclerosis. *J Clin Invest* 2014;124:1608-1621. PUBMED | CROSSREF
14. Zou HH, Wang L, Zheng XX, Xu GS, Shen Y. Endothelial cells secreted endothelin-1 augments diabetic nephropathy via inducing extracellular matrix accumulation of mesangial cells in $ETBR^{+}$ mice. *Aging (Albany NY)* 2019;11:1804-1820. PUBMED | CROSSREF

https://doi.org/10.5049/EBP.2026.24.e7

15. Lindahl P, Hellström M, Kalén M, et al. Paracrine PDGF-B/PDGF-Rbeta signaling controls mesangial cell development in kidney glomeruli. *Development* 1998;125:3313-3322. PUBMED | CROSSREF
16. Yuen DA, Stead BE, Zhang Y, et al. eNOS deficiency predisposes podocytes to injury in diabetes. *J Am Soc Nephrol* 2012;23:1810-1823. PUBMED | CROSSREF
17. Stockand JD, Sansom SC. Glomerular mesangial cells: electrophysiology and regulation of contraction. *Physiol Rev* 1998;78:723-744. PUBMED | CROSSREF
18. Bahadoran Z, Mirmiran P, Kashfi K, Ghasemi A. Vascular nitric oxide resistance in type 2 diabetes. *Cell Death Dis* 2023;14:410. PUBMED | CROSSREF
19. Wu XM, Gao YB, Cui FQ, Zhang N. Exosomes from high glucose-treated glomerular endothelial cells activate mesangial cells to promote renal fibrosis. *Biol Open* 2016;5:484-491. PUBMED | CROSSREF
20. Seo CW, Lee EY, Oh JS, Choi D. Urinary extracellular vesicle proteins for biomarker discovery in chronic kidney disease. *Kidney Res Clin Pract* 2026;45:36-49. PUBMED | CROSSREF
21. Wu X, Gao Y, Xu L, et al. Exosomes from high glucose-treated glomerular endothelial cells trigger the epithelial-mesenchymal transition and dysfunction of podocytes. *Sci Rep* 2017;7:9371. PUBMED | CROSSREF
22. Wang YY, Tang LQ, Wei W. Berberine attenuates podocytes injury caused by exosomes derived from high glucose-induced mesangial cells through TGFβ1-PI3K/AKT pathway. *Eur J Pharmacol* 2018;824:185-192. PUBMED | CROSSREF
23. Khan S, Lakhe-Reddy S, McCarty JH, et al. Mesangial cell integrin αvβ8 provides glomerular endothelial cell cytoprotection by sequestering TGF-β and regulating PECAM-1. *Am J Pathol* 2011;178:609-620. PUBMED | CROSSREF
24. Hartner A, Cordasic N, Menendez-Castro C, et al. Lack of α8-integrin aggravates podocyte injury in experimental diabetic nephropathy. *Am J Physiol Renal Physiol* 2010;299:F1151-F1157. PUBMED | CROSSREF
25. Makhammajanov Z, Gaipov A, Myngbay A, Bukasov R, Aljofan M, Kanbay M. Tubular toxicity of proteinuria and the progression of chronic kidney disease. *Nephrol Dial Transplant* 2024;39:589-599. PUBMED | CROSSREF
26. Eleftheriadis T, Pissas G, Golfinopoulos S, et al. Routes of albumin overload toxicity in renal tubular epithelial cells. *Int J Mol Sci* 2023;24:9640. PUBMED | CROSSREF
27. Wong DWL, Yiu WH, Chan KW, et al. Activated renal tubular Wnt/β-catenin signaling triggers renal inflammation during overload proteinuria. *Kidney Int* 2018;93:1367-1383. PUBMED | CROSSREF
28. Zhuang Y, Ding G, Zhao M, et al. NLRP3 inflammasome mediates albumin-induced renal tubular injury through impaired mitochondrial function. *J Biol Chem* 2014;289:25101-25111. PUBMED | CROSSREF
29. Rana R, Manoharan J, Elwakiel A, et al. Glomerular-tubular crosstalk via cold shock Y-box binding protein-1 in the kidney. *Kidney Int* 2024;105:65-83. PUBMED | CROSSREF
30. Chen SJ, Lv LL, Liu BC, Tang RN. Crosstalk between tubular epithelial cells and glomerular endothelial cells in diabetic kidney disease. *Cell Prolif* 2020;53:e12763. PUBMED | CROSSREF
31. Ren Y, Garvin JL, Liu R, Carretero OA. Role of macula densa adenosine triphosphate (ATP) in tubuloglomerular feedback. *Kidney Int* 2004;66:1479-1485. PUBMED | CROSSREF
32. León-Jiménez D, Sridhar VS, López-Mendoza M, et al. Kidney hemodynamic effects of sodium-glucose cotransporter 2 inhibitors in diabetes: physiology and clinical implications. *Clin Kidney J* 2025;18:sfae370. PUBMED | CROSSREF
33. Zha DQ, Gao P, Wu XY. Nicotinamide mononucleotide protects against diabetic nephropathy *via* IL-6/Rab5-mediated crosstalk between proximal tubular epithelial cells and podocytes. *World J Diabetes* 2025;16:109782. PUBMED | CROSSREF
34. Xu C, Zhou X, Xie T, et al. Renal tubular Bim mediates the tubule-podocyte crosstalk via NFAT2 to induce podocyte cytoskeletal dysfunction. *Theranostics* 2020;10:6806-6824. PUBMED | CROSSREF
35. Hasegawa K, Wakino S, Simic P, et al. Renal tubular Sirt1 attenuates diabetic albuminuria by epigenetically suppressing Claudin-1 overexpression in podocytes. *Nat Med* 2013;19:1496-1504. PUBMED | CROSSREF
36. Marchant V, Droguett A, Valderrama G, et al. Tubular overexpression of Gremlin in transgenic mice aggravates renal damage in diabetic nephropathy. *Am J Physiol Renal Physiol* 2015;309:F559-F568. PUBMED | CROSSREF
37. Lindenmeyer MT, Kretzler M, Boucherot A, et al. Interstitial vascular rarefaction and reduced VEGF-A expression in human diabetic nephropathy. *J Am Soc Nephrol* 2007;18:1765-1776. PUBMED | CROSSREF
38. Jacobs ME, de Vries DK, Engelse MA, Dumas SJ, Rabelink TJ. Endothelial to mesenchymal transition in kidney fibrosis. *Nephrol Dial Transplant* 2024;39:752-760. PUBMED | CROSSREF
39. Tsai YC, Kuo MC, Hung WW, et al. Proximal tubule-derived exosomes contribute to mesangial cell injury in diabetic nephropathy via miR-92a-1-5p transfer. *Cell Commun Signal* 2023;21:10. PUBMED | CROSSREF

40. Park PG, Hwang J, Kim Y, et al. Inflammatory milieu by crosstalk between glomerulus and proximal tubular cells in type 2 diabetes mellitus kidney disease. *Diabetes Metab J* 2025;49:1024-1039. PUBMED | CROSSREF
41. De Miguel C, Hamrick WC, Hobbs JL, Pollock DM, Carmines PK, Pollock JS. Endothelin receptor-specific control of endoplasmic reticulum stress and apoptosis in the kidney. *Sci Rep* 2017;7:43152. PUBMED | CROSSREF
42. Vallon V. State-of-the-art-review: mechanisms of action of SGLT2 inhibitors and clinical implications. *Am J Hypertens* 2024;37:841-852. PUBMED | CROSSREF
43. Jiang B, Cheng Z, Wang D, et al. Unveiling the podocyte-protective effect of sodium-glucose cotransporter-2 inhibitors. *Kidney Res Clin Pract* 2025;44:69-78. PUBMED | CROSSREF
44. Geng J, Ma S, Tang H, Zhang C. Pathogenesis and therapeutic perspectives of tubular injury in diabetic kidney disease: an update. *Biomedicines* 2025;13:1424. PUBMED | CROSSREF
45. Gangadharan Komala M, Gross S, Zaky A, Pollock C, Panchapakesan U. Linagliptin limits high glucose induced conversion of latent to active TGFß through interaction with CIM6PR and limits renal tubulointerstitial fibronectin. *PLoS One* 2015;10:e0141143. PUBMED | CROSSREF
46. Abdelrahman AM, Awad AS, Hasan I, Abdel-Rahman EM. Glucagon-like peptide-1 receptor agonists and diabetic kidney disease: from bench to bed-side. *J Clin Med* 2024;13:7732. PUBMED | CROSSREF
47. Al-Tantawy SM, Eraky SM, Eissa LA. Novel therapeutic target for diabetic kidney disease through downregulation of miRNA-192-5p and miRNA-21-5p by celastrol: implication of autophagy, oxidative stress, and fibrosis. *Naunyn Schmiedebergs Arch Pharmacol* 2025;398:6915-6928. PUBMED | CROSSREF
48. Cheng J, Zhang C. Mesenchymal stem cell therapy: therapeutic opportunities and challenges for diabetic kidney disease. *Int J Mol Sci* 2024;25:10540. PUBMED | CROSSREF
49. Kuo FC, Chao CT, Lin SH. The dynamics and plasticity of epigenetics in diabetic kidney disease: therapeutic applications vis-à-vis. *Int J Mol Sci* 2022;23:843. PUBMED | CROSSREF
50. Xi Y, Song W. Kidney organoids in translational research: disease modeling, drug discovery, and unresolved challenges. *Cell Tissue Res* 2025;402:303-312. PUBMED | CROSSREF

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Review Article

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The Role of Extracellular Vesicles in the Pathogenesis of Hypertension

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

ABSTRACT

Hypertension is one of the most common health problems and a leading global risk factor for cardiovascular, cerebrovascular, and renal diseases. The pathogenesis of essential hypertension is complex, and many organs, such as the heart, kidneys, arteries, and immune system, are involved in its pathophysiology. Extracellular vesicles (EVs) are membrane-bound nanosized structures that are generated and released into the extracellular fluid by all cell types. They mediate cell-to-cell communication in various physiological and pathophysiological processes. Therefore, EVs may play pivotal roles in the pathogenesis and systemic progression of diverse pathological conditions, including inflammatory, vascular, neoplastic, infectious, and neurodegenerative disorders. Emerging evidence has underscored their involvement in the development and progression of hypertension. Circulating and urinary EVs are promising diagnostic, prognostic, and therapeutic biomarkers of cardiovascular diseases, including hypertension. Moreover, EV-mediated therapies, particularly engineered EVs designed for precise drug delivery, are currently being developed for the treatment of various cardiovascular disorders, including hypertension and myocardial infarction. This review explores the role of EVs in the pathogenesis of hypertension and summarizes their potential as diagnostic and prognostic biomarkers.

Keywords: Biomarker; Exosomes; Hypertension; Pathology; Physiology

INTRODUCTION

Hypertension is defined as an elevation in systolic and/or diastolic blood pressure (BP) and remains a critical global health challenge, affecting an estimated 1.39 billion individuals worldwide [1]. The global prevalence of hypertension continues to increase, driven primarily by an aging population and growing exposure to life-related risks [2]. Hypertension is the most relevant cardiovascular risk factor and an important contributor to morbidity and mortality worldwide [3,4]. Essential hypertension accounts for more than 90% of all hypertension cases [5], but its exact pathogenesis has not been fully elucidated. Recent studies have shown that extracellular vesicles (EVs) contribute to both normal physiological processes and the development of cardiovascular diseases (CVDs), including hypertension, by regulating arterial and renal function [6].

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EVs are membrane-enclosed particles released by cells under both physiological and pathological conditions and are typically classified as exosomes, microvesicles, or apoptotic bodies based on their distinct biogenesis [7]. By transferring biomolecules—such as proteins, lipids, and nucleic acids—while protecting this cargo from degradation, EVs facilitate sophisticated cell-to-cell communication [8]. Due to their inherent tissue or cell-type specificity, EVs have emerged as significant diagnostic and prognostic biomarkers for various diseases [9]. Recent evidence suggests that circulating and urinary EVs serve as promising biomarkers for CVD [6,10]. Quantitative and qualitative alterations in these vesicles are increasingly associated with the pathogenesis of CVDs such as hypertension, heart failure, and atrial fibrillation [10,11]. In particular, exploring the molecular cargo within EVs provides crucial insights into the pathogenesis of essential hypertension, as it reflects systemic vascular inflammation, endothelial dysfunction, and renal stress that drive BP elevation [12].

Here, we review the fundamental features of EVs and summarize key studies investigating their role in hypertension. Furthermore, we evaluate the clinical potential of EVs as diagnostic and prognostic biomarkers of hypertension.

OVERVIEW OF EVs

Biogenesis and classification of EVs

EVs are a heterogeneous family of lipid bilayer-enclosed spherical particles released by cells under both physiological and pathological conditions. They are classified as exosomes, microvesicles, or apoptotic bodies, based on their biogenesis, size, and surface markers (**Fig. 1**) [7]. EVs are readily detectable in various biofluids, including blood, urine, saliva,

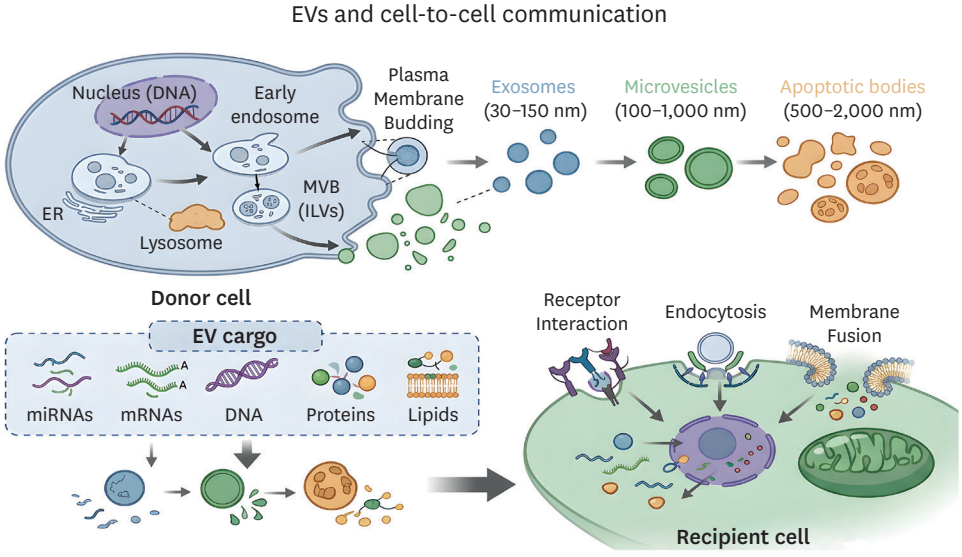

Fig. 1. Biogenesis and transport of EVs. Based on their size and secretory origin, EVs are categorized as exosomes, microvesicles, and apoptotic bodies. They contain different materials, including many functional molecules, such as miRNAs, mRNAs), lncRNAs, proteins, DNA fragments, and lipids. These molecules are involved in intercellular communication, elicit changes in intracellular signaling pathways, and play a role in the pathogenesis of various diseases, including hypertension.
ER, endoplasmic reticulum; EV, extracellular vesicle; ILV, intraluminal vesicle; mRNA, messenger RNA; miRNA, microRNA; MVB, multivesicular body; ncRNA, long noncoding RNA.

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and bronchoalveolar lavage fluid [9]. Initially, they were thought to be cellular debris, also known as "cell dust," with no biological significance [13]. However, subsequent studies have indicated that they play an important role in regulating a wide range of normal cellular physiological processes [8]. EVs carry a variety of functional molecules, including RNAs (microRNA, messenger RNA, and long noncoding RNA), proteins, DNA fragments, and lipids, which serve as intercellular messengers [14]. These cargoes can be delivered to both neighboring and distant recipient cells, where they potentially reprogram cellular functions and gene expression.

EV isolation

The isolation and purification of EVs have gained significant traction because of their potential as transformative tools for the diagnosis and treatment of various human diseases. However, the isolation process requires careful consideration of several factors to ensure its purity and functionality. The most widely used method for EV isolation is differential centrifugation, which separates vesicle particles based on their size and density by sequentially increasing the centrifugal force to pellet cells and debris [15]. In addition to differential centrifugation, other methods have been developed for EV isolation. These methods include density gradient centrifugation, size-exclusion chromatography, ultrafiltration, immunocapture, and various precipitation-based methods using different reagents [16]. In recent years, various commercial precipitation-based reagents have been introduced into the market. Kits such as ExoQuick-TC™ and Total Exosome Isolation Reagent (Invitrogen™, Carlsbad, CA, USA) are based on aggregating agents followed by low-speed centrifugation [17].

MULTIFACETED ROLES OF EVs IN THE PATHOGENESIS OF HYPERTENSION

Hypertension is one of the most common health problems worldwide and a major risk factor for CVD [3,4]. The pathogenesis of primary hypertension remains poorly understood and involves multiple organs and systems, including the heart, arteries, and kidneys [18]. A growing body of evidence suggests that EVs are associated with the pathophysiology of hypertension [17].

Renal mechanism

The kidney is a pivotal organ in the maintenance of systemic BP. Since the initial identification of urinary EVs in 2004, interest has surged in understanding how these urinary EVs serve as key players in the onset of hypertension and as potential tools for identifying the disease [19,20]. Urinary EV analysis in hypertensive patients has largely targeted the distal convoluted tubule sodium chloride cotransporter (NCC), which is vital for salt balance and BP control. NCC overactivation enhances sodium chloride reabsorption in the renal tubules, which in turn elevates BP [21]. Studies have investigated whether the concentration of sodium transporters in urinary EVs reflects the actual rate of renal sodium reabsorption under normal physiological conditions. Elevated levels of total and phosphorylated NCC have been observed in the urinary EVs of patients with hypertension associated with either pseudohypoaldosteronism type II or tacrolimus treatment following kidney transplantation [22,23]. In contrast, Esteva-Font et al. [24] did not observe any difference in NCC abundance between cyclosporine-treated transplant recipients (n = 39) and non-calcineurin inhibitor immunosuppressant recipients (n = 8).

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The epithelial sodium channel (ENaC), situated in the apical membrane of the connecting tubule and collecting duct, mediates sodium reabsorption. Increased concentrations of proteolytically cleaved γ-ENaC were observed in the urinary EVs of patients with diabetic nephropathy and hypertension [25]. Qi et al. [26] demonstrated that both dietary sodium restriction and acute aldosterone administration significantly elevated γ-ENaC concentrations in urinary EVs, while NCC and α-ENaC remained unaffected. Consequently, urinary exosomal γ-ENaC may be utilized as a specific biomarker to assess ENaC activation.

The sodium-hydrogen exchanger type 3 (NHE3) serves as the primary mediator of apical sodium reabsorption in the renal proximal tubule. Overactivation of NHE3 leads to excessive sodium retention, increased blood volume, and ultimately, elevated BP. The activity of NHE3 within urinary EVs serves as a valuable marker for assessing renal sodium handling. According to Tonneijck et al. [27], the abundance of phosphorylated NHE3 in urinary EVs correlates with renal physiological responses, suggesting its potential as a surrogate marker for monitoring hypertensive treatment efficacy.

Renin-angiotensin system (RAS)

Dysregulation of sodium and water homeostasis, mediated by the RAS, is a fundamental pathophysiological mechanism in the development of hypertension [28]. The RAS consists of 2 distinct pathways: classical and counter-regulatory [29]. The classical pathway stimulates vasoconstriction and renal sodium transport. However, the non-classical pathway offsets these actions. Angiotensin-converting enzyme (ACE) 2 converts angiotensin II to angiotensin 1–7, effectively opposing the classical system. Compared with adventitial fibroblast-derived EVs in normotensive rats, those in hypertensive rats exhibited significantly elevated ACE levels, whereas angiotensin II and angiotensin II type 1 receptor (AT1R) concentrations remain comparable [30]. This enriched ACE content in hypertensive rat-derived EVs triggers angiotensin II production and subsequent AT1R activation, ultimately driving vascular smooth muscle cells (VSMCs) migration. Cardiac biomechanical stress, such as pressure overload, triggers the secretion of exosomes containing functional AT1Rs from cardiomyocytes [31]. The administration of AT1R-enriched exosomes to AT1R-knockout mice results in their targeted trafficking to cardiac and skeletal myocytes, as well as resistance vessels, thereby reconstituting the pressor response to angiotensin II.

Endothelial dysfunction

Endothelial cells maintain systemic hemostasis and BP by producing vasodilatory factors and by providing antioxidants and anti-inflammatory agents. Therefore, endothelial dysfunction, primarily characterized by decreased endothelial nitric oxide production and increased superoxide levels, is associated with the development of arterial hypertension [32]. Elevated levels of endothelial microparticles have been observed in individuals with hypertension, reflecting underlying endothelial dysfunction. Furthermore, these levels correlate positively with systolic BP and pulse wave velocity [33,34]. Recent findings have underscored the critical role of inflammatory mechanisms, spanning innate and adaptive immunity, in the pathogenesis and clinical outcomes of atherosclerosis [35]. In hypertension, EVs originating from activated immune cells and platelets facilitate the progression of vascular impairment by transferring pro-inflammatory cytokines, signaling receptors, and regulatory RNAs to recipient cells. In vitro, cytokines released from leukocyte or platelet microparticles increase the expression of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin, which activate endothelial cell adhesion

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molecules and nuclear factor-κB-dependent pathways, therefore promoting an inflammatory response in endothelial cells [36]. In the clinical setting, Lugo-Gavidia et al. [37] proposed circulating platelet-derived EVs as reliable biomarkers for assessing vascular health. Monocyte miR-27a in EVs decreases Mas receptor expression and endothelial nitric oxide synthase phosphorylation in the endothelium, impairing Ang-(1–7)-mediated vasodilation and causing hypertension [38]. Understanding the contribution of EVs to the pathogenesis of hypertension may facilitate their use as diagnostic biomarkers.

Vascular remodeling and inflammation

Ample evidence suggests that hypertension leads to vascular remodeling, which is characterized by a thickened smooth muscle layer and an elevated media-to-lumen ratio [39]. These structural changes are thought to stem from pathological shifts in both VSMCs and adventitial structures [40]. EVs contribute to the thickening of vascular smooth muscle layers and remodeling of the adventitia through diverse mechanism [41]. A study by Vajen et al. [42] showed that platelet-derived EVs act as potent immunomodulators by facilitating monocyte adhesion to VSMCs and engaging with CD40 and P-selectin. This interaction induces a phenotypic switch toward a pro-inflammatory state, subsequently triggering the proliferation and migration of VSMCs. Wang et al. [43] reported that endothelial-derived microRNA-92a transported via EVs promotes arterial stiffness and hypertension by triggering a phenotypic switch in VSMCs from a contractile to a proliferate state.

Oxidative stress

Oxidative stress is increasingly recognized as a cornerstone in the pathogenesis of hypertension, and serves as a trigger for the liberation of EVs, which in turn exacerbate oxidative damage. Research by Burger et al. [44] identified that angiotensin II-mediated EV release is driven by nicotinamide adenine dinucleotide phosphate oxidase (NOX) and reactive oxygen species (ROS) via Rho kinase-targeted lipid rafts. Once released, these EVs promote a pro-inflammatory environment and stimulate ROS formation within the endothelium. While ROS are essential for maintaining vascular wall homeostasis, their dysregulation significantly drives the hypertensive process. By regulating NOX2 expression, miR-34a acts as a critical mediator of oxidative stress, subsequently driving ROS production [45]. Its elevated presence in the circulation and exosomes of hypertensive patients suggests that it plays a pivotal role in modulating systemic inflammatory responses. Furthermore, the detection of miR-34a in both plasma and exosomes underscores its potential as a key signaling molecule that promotes vascular inflammation in hypertension. However, the role of EVs in hypertension is not exclusively detrimental; they also serve as conduits for protective signaling to counteract vascular injury. Notably, EVs released under oxidative stress serve as vehicles for antioxidant molecules, including nuclear factor erythroid 2-related factor-2 (Nrf2). As a redox-sensitive transcription factor, Nrf2 acts as a master regulator of the cellular antioxidant response by binding to Antioxidant Response Element sites [46]. These findings suggest that EVs function as a sophisticated regulatory platform that can either propagate oxidative damage or initiate protective counter-mechanisms in the hypertensive vasculature.

THERAPEUTIC POTENTIAL OF EVs IN HYPERTENSION

The pivotal role of EVs in cardiovascular health and disease has attracted significant interest owing to their therapeutic applications [6]. In particular, the regenerative potential of stem

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cell-derived EVs, especially those derived from mesenchymal stem cells, has emerged as a key focus [47]. Several studies have demonstrated that exosomes from diverse sources can promote post-myocardial infarction angiogenesis through multifaceted mechanisms [47,48]. Beyond their innate bioactivity, EVs are being pioneered as targeted drug delivery systems. By leveraging their natural homing capabilities, they can deliver therapeutic agents directly to damaged cardiac tissues while minimizing systemic off-target effects [49]. Although research on EVs has advanced rapidly across various cardiovascular conditions, their specific utility in treating essential hypertension remains relatively underexplored. Notably, a recent animal study revealed that plasma-derived EVs possess the capacity to regulate systemic BP and mitigate hypertension-induced end-organ damage [50]. Future investigations are likely to elucidate how these EV-based platforms can be further optimized for clinical BP management.

CONCLUSION

Hypertension is an independent risk factor for the future incidence of major cardiovascular and kidney disorders. The exact pathophysiology of primary hypertension is not fully understood; however, EVs have provided novel insights into its development (**Fig. 2**). Further investigations are warranted to elucidate the role of EVs in the pathogenesis of hypertension. Identifying EV-derived components that modulate BP may pave the way for novel preventive

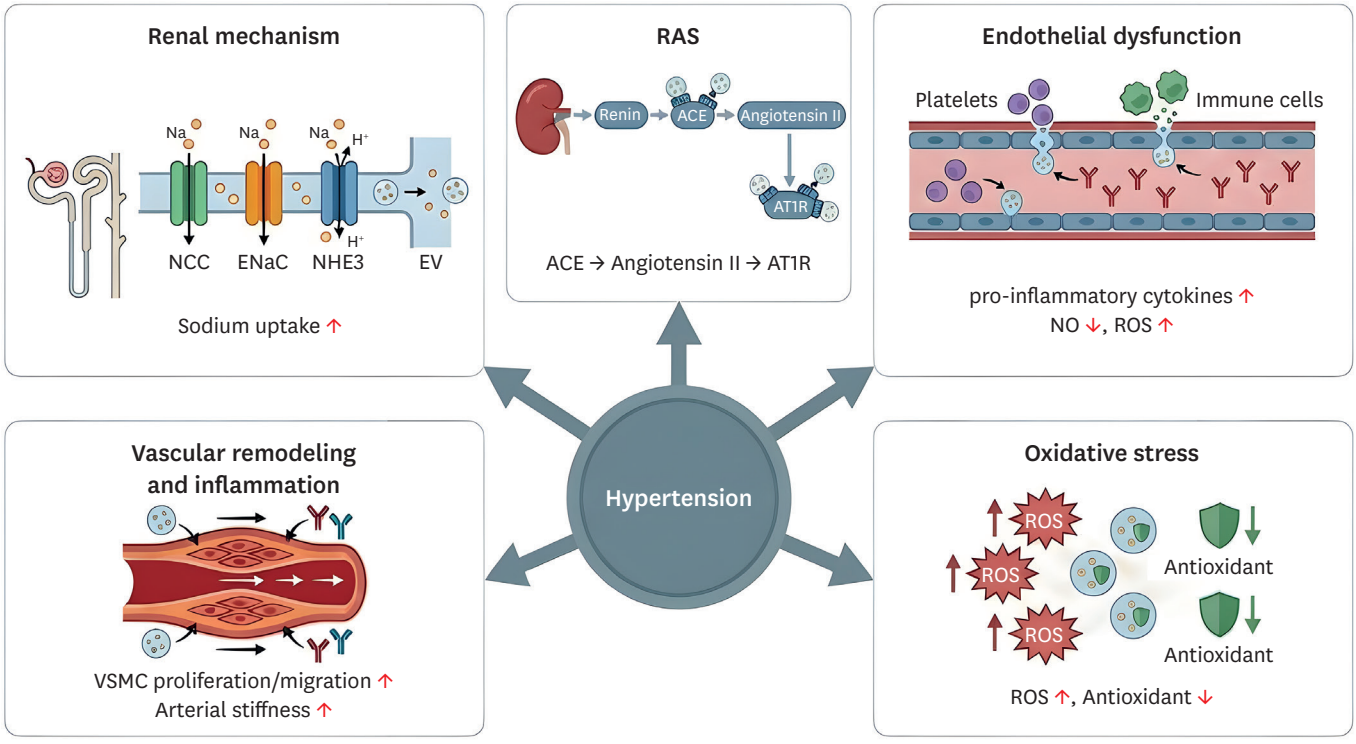

Fig. 2. Role of EVs in the development and progression of hypertension. Hypertension-related risk factors stimulate the release of systemic and urinary EVs, which are critical mediators of vascular and renal dysfunction. These vesicles are released by various cells and contribute to the pathogenesis of hypertension by inducing endothelial dysfunction, oxidative stress, VSMC proliferation/migration, and alterations in renal Na^+ transport mechanisms (NHE3, NCC, and ENaC). Furthermore, EV activation has been linked to maladaptive RAS changes that accelerate the progression of hypertension.
ACE, angiotensin-converting enzyme; AT1R, angiotensin II type 1 receptor; ENaC, epithelial sodium channel; EV, extracellular vesicle; NCC, sodium chloride cotransporter; NHE3, sodium-hydrogen exchanger type 3; NO, nitric oxide; RAS, renin-angiotensin system; ROS, reactive oxygen species; VSMC, vascular smooth muscle cell.

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and therapeutic strategies. The therapeutic application of EVs in hypertension faces distinct challenges, primarily due to the multifaceted pathophysiology of hypertension, as well as the high efficacy and cost-effectiveness of existing pharmacological treatments. To overcome these hurdles, future research must focus on enhancing the target-specificity of EVs and demonstrating their superior clinical benefits over conventional therapies. Moreover, the discovery of specific EV biomarkers is essential for the early detection of hypertension before the manifestation of target organ damage.

REFERENCES

1. Mills KT, Bundy JD, Kelly TN, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation* 2016;134:441-450. PUBMED | CROSSREF
2. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol* 2020;16:223-237. PUBMED | CROSSREF
3. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;392:1923-1994. PUBMED | CROSSREF
4. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;392:1736-1788. PUBMED | CROSSREF
5. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;42:3227-3337. PUBMED | CROSSREF
6. Yang J, Zou X, Jose PA, Zeng C. Extracellular vesicles: potential impact on cardiovascular diseases. *Adv Clin Chem* 2021;105:49-100. PUBMED | CROSSREF
7. Hessvik NP, Llorente A. Current knowledge on exosome biogenesis and release. *Cell Mol Life Sci* 2018;75:193-208. PUBMED | CROSSREF
8. Camussi G, Deregibus MC, Bruno S, Cantaluppi V, Biancone L. Exosomes/microvesicles as a mechanism of cell-to-cell communication. *Kidney Int* 2010;78:838-848. PUBMED | CROSSREF
9. Yáñez-Mó M, Siljander PR, Andreu Z, et al. Biological properties of extracellular vesicles and their physiological functions. *J Extracell Vesicles* 2015;4:27066. PUBMED | CROSSREF
10. Cappucci IP, Tremoli E, Zavan B, Ferroni L. Circulating extracellular vesicles in cardiovascular disease. *Int J Mol Sci* 2025;26:6817. PUBMED | CROSSREF
11. Li T, Wang W, Qin Z, et al. Extracellular vesicles in cardiovascular diseases: pathogenic mediators, diagnostic tools, and therapeutic vectors. *Front Cardiovasc Med* 2025;12:1666589. PUBMED | CROSSREF
12. Liu ZZ, Jose PA, Yang J, Zeng C. Importance of extracellular vesicles in hypertension. *Exp Biol Med (Maywood)* 2021;246:342-353. PUBMED | CROSSREF
13. Wolf P. The nature and significance of platelet products in human plasma. *Br J Haematol* 1967;13:269-288. PUBMED | CROSSREF
14. Huang-Doran I, Zhang CY, Vidal-Puig A. Extracellular vesicles: novel mediators of cell communication in metabolic disease. *Trends Endocrinol Metab* 2017;28:3-18. PUBMED | CROSSREF
15. Théry C, Amigorena S, Raposo G, Clayton A. Isolation and characterization of exosomes from cell culture supernatants and biological fluids. *Curr Protoc Cell Biol* 2006;Chapter 3:Unit 3.22. PUBMED | CROSSREF
16. Merchant ML, Rood IM, Deegens JKJ, Klein JB. Isolation and characterization of urinary extracellular vesicles: implications for biomarker discovery. *Nat Rev Nephrol* 2017;13:731-749. PUBMED | CROSSREF
17. Musante L, Bontha SV, La Salvia S, et al. Rigorous characterization of urinary extracellular vesicles (uEVs) in the low centrifugation pellet - a neglected source for uEVs. *Sci Rep* 2020;10:3701. PUBMED | CROSSREF
18. Yang J, Villar VA, Armando I, Jose PA, Zeng C. G protein-coupled receptor kinases: crucial regulators of blood pressure. *J Am Heart Assoc* 2016;5:e003519. PUBMED | CROSSREF
19. Pisitkun T, Shen RF, Knepper MA. Identification and proteomic profiling of exosomes in human urine. *Proc Natl Acad Sci U S A* 2004;101:13368-13373. PUBMED | CROSSREF
20. Sun IO, Santelli A, Abumoawad A, et al. Loss of renal peritubular capillaries in hypertensive patients is detectable by urinary endothelial microparticle levels. *Hypertension* 2018;72:1180-1188. PUBMED | CROSSREF

https://doi.org/10.5049/EBP.2026.24.e8

21. Castagna A, Mango G, Martinelli N, et al. Sodium chloride cotransporter in hypertension. *Biomedicines* 2024;12:2580. PUBMED | CROSSREF

22. Rojas-Vega L, Jiménez-Vega AR, Bazúa-Valenti S, et al. Increased phosphorylation of the renal Na^+-Cl^- cotransporter in male kidney transplant recipient patients with hypertension: a prospective cohort. *Am J Physiol Renal Physiol* 2015;309:F836-F842. PUBMED | CROSSREF

23. Mayan H, Attar-Herzberg D, Shaharabany M, Holtzman EJ, Farfel Z. Increased urinary Na-Cl cotransporter protein in familial hyperkalaemia and hypertension. *Nephrol Dial Transplant* 2008;23:492-496. PUBMED | CROSSREF

24. Esteva-Font C, Guillén-Gómez E, Diaz JM, et al. Renal sodium transporters are increased in urinary exosomes of cyclosporine-treated kidney transplant patients. *Am J Nephrol* 2014;39:528-535. PUBMED | CROSSREF

25. Andersen H, Friis UG, Hansen PB, Svenningsen P, Henriksen JE, Jensen BL. Diabetic nephropathy is associated with increased urine excretion of proteases plasmin, prostasin and urokinase and activation of amiloride-sensitive current in collecting duct cells. *Nephrol Dial Transplant* 2015;30:781-789. PUBMED | CROSSREF

26. Qi Y, Wang X, Rose KL, et al. Activation of the endogenous renin-angiotensin-aldosterone system or aldosterone administration increases urinary exosomal sodium channel excretion. *J Am Soc Nephrol* 2016;27:646-656. PUBMED | CROSSREF

27. Tonneijck L, Muskiet MHA, Blijdorp CJ, et al. Renal tubular effects of prolonged therapy with the GLP-1 receptor agonist lixisenatide in patients with type 2 diabetes mellitus. *Am J Physiol Renal Physiol* 2019;316:F231-F240. PUBMED | CROSSREF

28. Almeida LF, Tofteng SS, Madsen K, Jensen BL. Role of the renin-angiotensin system in kidney development and programming of adult blood pressure. *Clin Sci (Lond)* 2020;134:641-656. PUBMED | CROSSREF

29. Kobori H, Nangaku M, Navar LG, Nishiyama A. The intrarenal renin-angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. *Pharmacol Rev* 2007;59:251-287. PUBMED | CROSSREF

30. Ren XS, Tong Y, Qiu Y, et al. MiR155-5p in adventitial fibroblasts-derived extracellular vesicles inhibits vascular smooth muscle cell proliferation via suppressing angiotensin-converting enzyme expression. *J Extracell Vesicles* 2020;9:1698795. PUBMED | CROSSREF

31. Pironti G, Strachan RT, Abraham D, et al. Circulating exosomes induced by cardiac pressure overload contain functional angiotensin II type 1 receptors. *Circulation* 2015;131:2120-2130. PUBMED | CROSSREF

32. Versari D, Daghini E, Virdis A, Ghiadoni L, Taddei S. Endothelium-dependent contractions and endothelial dysfunction in human hypertension. *Br J Pharmacol* 2009;157:527-536. PUBMED | CROSSREF

33. Sansone R, Baaken M, Horn P, et al. Endothelial microparticles and vascular parameters in subjects with and without arterial hypertension and coronary artery disease. *Data Brief* 2018;19:495-500. PUBMED | CROSSREF

34. Lugo-Gavidia LM, Burger D, Nolde JM, Matthews VB, Schlaich MP. Evaluation of circulating platelet extracellular vesicles and hypertension mediated organ damage. *Int J Mol Sci* 2022;23:15150. PUBMED | CROSSREF

35. Libby P, Buring JE, Badimon L, et al. Atherosclerosis. *Nat Rev Dis Primers* 2019;5:56. PUBMED | CROSSREF

36. Lovren F, Verma S. Evolving role of microparticles in the pathophysiology of endothelial dysfunction. *Clin Chem* 2013;59:1166-1174. PUBMED | CROSSREF

37. Lugo-Gavidia LM, Carnagarin R, Burger D, et al. Circulating platelet-derived extracellular vesicles correlate with night-time blood pressure and vascular organ damage and may represent an integrative biomarker of vascular health. *J Clin Hypertens (Greenwich)* 2022;24:738-749. PUBMED | CROSSREF

38. Zou X, Wang J, Chen C, et al. Secreted monocyte miR-27a, via mesenteric arterial mas receptor-eNOS pathway, causes hypertension. *Am J Hypertens* 2020;33:31-42. PUBMED | CROSSREF

39. Aalkjaer C, Heagerty AM, Petersen KK, Swales JD, Mulvany MJ. Evidence for increased media thickness, increased neuronal amine uptake, and depressed excitation--contraction coupling in isolated resistance vessels from essential hypertensives. *Circ Res* 1987;61:181-186. PUBMED | CROSSREF

40. Duca L, Blaise S, Romier B, et al. Matrix ageing and vascular impacts: focus on elastin fragmentation. *Cardiovasc Res* 2016;110:298-308. PUBMED | CROSSREF

41. Buffolo F, Monticone S, Camussi G, Aikawa E. Role of extracellular vesicles in the pathogenesis of vascular damage. *Hypertension* 2022;79:863-873. PUBMED | CROSSREF

42. Vajen T, Benedikter BJ, Heinzmann ACA, et al. Platelet extracellular vesicles induce a pro-inflammatory smooth muscle cell phenotype. *J Extracell Vesicles* 2017;6:1322454. PUBMED | CROSSREF

43. Wang C, Wu H, Xing Y, et al. Endothelial-derived extracellular microRNA-92a promotes arterial stiffness by regulating phenotype changes of vascular smooth muscle cells. *Sci Rep* 2022;12:344. PUBMED | CROSSREF

44. Burger D, Montezano AC, Nishigaki N, He Y, Carter A, Touyz RM. Endothelial microparticle formation by angiotensin II is mediated via Ang II receptor type I/NADPH oxidase/Rho kinase pathways targeted to lipid rafts. *Arterioscler Thromb Vasc Biol* 2011;31:1898-1907. PUBMED | CROSSREF

45. Li SZ, Hu YY, Zhao J, et al. MicroRNA-34a induces apoptosis in the human glioma cell line, A172, through enhanced ROS production and NOX2 expression. *Biochem Biophys Res Commun* 2014;444:6-12. PUBMED | CROSSREF

46. Kahroba H, Davatgaran-Taghipour Y. Exosomal Nrf2: from anti-oxidant and anti-inflammation response to wound healing and tissue regeneration in aged-related diseases. *Biochimie* 2020;171-172:103-109. PUBMED | CROSSREF

47. Ma T, Chen Y, Chen Y, et al. MicroRNA-132, delivered by mesenchymal stem cell-derived exosomes, promote angiogenesis in myocardial infarction. *Stem Cells Int* 2018;2018:3290372. PUBMED | CROSSREF

48. Liang X, Zhang L, Wang S, Han Q, Zhao RC. Exosomes secreted by mesenchymal stem cells promote endothelial cell angiogenesis by transferring miR-125a. *J Cell Sci* 2016;129:2182-2189. PUBMED | CROSSREF

49. Wang Z, Mo H, He Z, Chen A, Cheng P. Extracellular vesicles as an emerging drug delivery system for cancer treatment: current strategies and recent advances. *Biomed Pharmacother* 2022;153:113480. PUBMED | CROSSREF

50. Otani K, Yokoya M, Kodama T, et al. Plasma exosomes regulate systemic blood pressure in rats. *Biochem Biophys Res Commun* 2018;503:776-783. PUBMED | CROSSREF

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Original Article

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Patient and Clinician Perspectives on Hyperkalemia Management Under Cardio-Kidney-Protective Therapy: A Three-Stakeholder Cross-Sectional Survey

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ABSTRACT

Background: Maintaining renin–angiotensin system inhibitor (RASi) and mineralocorticoid receptor antagonist (MRA) therapy in patients with hyperkalemia is now favored by contemporary guidelines, yet the perspectives of patients and clinicians on this shift have rarely been examined in parallel.
Methods: We conducted three parallel descriptive cross-sectional surveys in Korea between April and May 2026: a patient survey distributed through a kidney-disease patient community; a nephrologist survey; and a multispecialty physician survey. Patients, nephrology specialists, and multispecialty physicians were analyzed separately and in a combined nephrologist-versus-non-nephrologist comparison.
Results: A total of 125 patients, 82 nephrologists, and 255 multispecialty physicians completed the survey. Patient awareness of hyperkalemia was high (perceived risk, 3.97; 95% confidence interval, 3.84–4.10). More patients preferred potassium-lowering medication (68.8%) over strict dietary control (31.2%) for hyperkalemia management. Clinicians rated maintenance of RASi and MRA as 3.81 (3.72–3.90) and 3.47 (3.37–3.56), respectively; nephrologists rated maintenance as more important than non-nephrologists for both classes ($p < 0.001$ for RASi, $p = 0.006$ for MRA). For long-term outpatient hyperkalemia, nephrologists most often endorsed prescribing a potassium binder (68.2%), while non-nephrologists most often endorsed reducing or discontinuing the culprit drugs (55.5%).
Conclusion: Patients preferred to maintain cardio-kidney-protective therapy. A specialty gap in this preference was observed between nephrologists and non-nephrology clinicians, indicating a need to broaden clinician awareness of the full spectrum of hyperkalemia management options, including the more active use of potassium-lowering agents.

Keywords: Chronic kidney disease; Hyperkalemia; Mineralocorticoid receptor antagonists; Questionnaires and surveys; Angiotensin receptor antagonists

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Conflicts of interest
All authors have no conflicts of interest to declare.

Data sharing statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions
Conceptualization: YY, SK; Data curation: YY; Formal analysis: YY; Funding acquisition: SK; Investigation: SHB, JL, SK; Methodology: YY, SHB, JL; Project administration: SK; Resources: SK; Supervision: SHB, JL, SK; Visualization: YY; Writing - original draft: YY; Writing - review & editing: YY.

INTRODUCTION

Hyperkalemia is one of the most common electrolyte abnormalities in clinical practice in patients with chronic kidney disease (CKD) [1]. Its prevalence rises with declining kidney function, affecting up to one in five patients at CKD stage 4 and approximately one in three at stage 5 [2,3]. Even modest elevations have been associated with malignant arrhythmia, sudden cardiac arrest, and excess all-cause mortality [4]. Many patients with CKD also have diabetes mellitus, hypertension, and cardiovascular disorders, particularly heart failure [5,6]. Guideline-directed therapy for these conditions relies on renin–angiotensin system inhibitors (RASis) and mineralocorticoid receptor antagonists (MRAs), both of which improve cardio-kidney outcomes but impair renal potassium excretion [7]. Withdrawal of these cardio-kidney-protective agents in response to hyperkalemia has been linked to worse long-term outcomes [8-10].

Conventional management of hyperkalemia has combined down-titration or withdrawal of contributing drugs, low-potassium dietary education, diuretics, sodium bicarbonate, and oral potassium binders [11]. The first-generation binders—calcium polystyrene sulfonate (CPS) and sodium polystyrene sulfonate (SPS)—are limited by palatability issues, constipation, and rare cases of bowel necrosis [12]. The 2024 Kidney Disease: Improving Global Outcomes (KDIGO) CKD guideline and the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America heart failure guideline now favor maintaining cardio-kidney-protective therapy whenever potassium can be controlled by other managements [13-15], a shift that the newer potassium binders, sodium zirconium cyclosilicate (SZC) and patiromer, have made practical by maintaining normokalemia and supporting higher RASi/MRA persistence in phase III and real-world studies [16-18]. Although management guidelines have changed, the perspectives of the stakeholders most directly affected—patients with kidney-related diagnoses and the clinicians who treat them—have rarely been examined in parallel within a single national context.

We therefore conducted a nationwide descriptive cross-sectional survey of knowledge, attitudes, and practices (KAP) among three Korean clinical stakeholder groups: patients with kidney-related diagnoses and prior hyperkalemia care, nephrology specialists, and a multispecialty physician group. This study aimed to characterize the current state of awareness, perceived risk, and real-world management of hyperkalemia, and to identify where patient-side perception and clinician-side practice diverge.

METHODS

Study design

This survey study comprised three parallel, descriptive cross-sectional KAP surveys conducted in Korea between April and May 2026: a survey of patients with kidney-related diagnoses (Survey A), a survey of nephrology specialists (Survey B), and a survey of physicians spanning a range of clinical specialties (Survey C). Each survey was delivered electronically, completed anonymously, and analyzed separately, with pre-specified comparisons between corresponding items on the clinician questionnaires (B and C) and between aggregated clinician and patient responses on selected awareness items. Reporting of the study followed the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) recommendations (**Supplementary Table 1**) [19].

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Patient survey (Survey A)

Participants for Survey A were recruited through a Korean online patient advocacy community for kidney disease, hosted as a moderated forum. The Korean Society of Nephrology (KSN) supported the study by posting the announcement and an anonymous survey link within the community for the duration of data collection, which corresponds to convenience sampling through an online patient community—an approach previously shown to yield substantial sample sizes for chronic-disease research while lowering the geographic and mobility barriers of clinic-based recruitment [20]. Individuals were eligible if they self-identified as a patient with a kidney-related diagnosis or as a family caregiver of such a patient, and reported a previous diagnosis of or treatment for hyperkalemia. Respondents who did not meet either criterion at the screening stage were not advanced to the substantive questionnaire. The instrument was co-developed by the research team and Korea Gallup, a professional survey organization, and was administered in Korean through Korea Gallup's secure web-based platform. It followed a sequential flow of six thematic sections covering patient background; awareness of and risk perception of hyperkalemia; self-rated familiarity with three drug- or diet-related contributors to hyperkalemia; experience with cardio-kidney-protective therapy; hyperkalemia care experience; and potassium binder experience and treatment preference.

Nephrologist survey (Survey B)

Survey B was distributed by the Korean nephrologist group at KSN. The study purpose and a single-click survey link were circulated via email to nephrology specialists registered with the society, and the questionnaire was hosted on Korea Gallup's secure web-based platform. Baseline characteristics captured at the start of the questionnaire included the volume of patients with hyperkalemia seen each month, the type of practice setting (clinic, hospital, general hospital, or tertiary/teaching hospital), and the number of years in clinical practice as a nephrologist.

Multispecialty physician survey (Survey C)

Survey C targeted the physician community of Korea through the Korean Medical Association (KMA). The official online news outlet of the KMA posted the study announcement and an embedded survey link as a banner notice on its portal for the duration of data collection; the questionnaire was hosted directly on the survey platform. In addition to the baseline characteristics captured in Survey B, Survey C respondents reported their primary clinical specialty, choosing from one of seven categories: nephrology, cardiology, endocrinology, other internal medicine subspecialty, family medicine, emergency medicine, or other.

Content shared between clinician surveys

Surveys B and C used an identical substantive item set spanning content domains, allowing direct between-group comparison on each matched item. The first domain captured awareness of the hyperkalemia threshold at which the respondent initiates intervention, as well as the factors most commonly perceived to provoke hyperkalemia in routine practice. The second domain examined how clinicians balance continuation of cardio-kidney-protective therapy against potassium control: respondents rated the importance of preserving RASi or MRA therapy in the face of recurrent hyperkalemia and reported the frequency with which they pursue three alternative responses to a hyperkalemic episode—dose reduction, drug discontinuation, or maintenance of the existing dose in combination with a potassium-lowering agent—separately for RASi and for MRA. The third domain addressed acute and chronic management: the first-line action when severe hyperkalemia is

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strongly suspected, the long-term strategy preferred for chronic or recurrent hyperkalemia in the outpatient setting, and the perceived feasibility of achieving stable control through dietary education alone. The fourth domain explored perceptions of potassium-binding agents: the principal limitations of the first-generation binders (CPS, SPS), the perceived clinical advantages of the newer binders (SZC, patiromer), and the practical barriers most commonly encountered when prescribing the newer agents.

Data quality

Multiple integrity checks were embedded in all three surveys to discourage fraudulent or duplicate participation, in line with recommendations for the conduct and reporting of internet-based health surveys [21]. In Survey A, eligibility was first verified through screening items on hyperkalemia diagnosis and prior treatment history; each participant additionally provided the name of the treating institution and the attending clinician, and responses with implausible or internally inconsistent entries were removed during data cleaning. A small set of follow-up items required knowledge consistent with actual hyperkalemia care (for example, the type of potassium binder previously prescribed), and respondents whose answers were incompatible with prior hyperkalemia treatment were excluded from the analytic sample. In Survey B, distribution was restricted to the KSN membership list, providing intrinsic verification of nephrology specialist status. In Survey C, access was restricted to the KMA members; respondents who did not select a clinical specialty or who reported never having managed hyperkalemia were excluded from the substantive analyses. To minimize the risk of duplicate participation, a single piece of contact information (a mobile phone number used for honorarium payment) was collected by the survey-administration companies—Korea Gallup (Surveys A and B) and the Korean Medical Times (Survey C)—and was used internally by those companies to deduplicate submissions; this contact information was never shared with the research team and was not used in any analyses.

Survey instruments and item formats

To minimize the risk of re-identification, Survey A recorded age in 10-year strata (< 20, 20s, 30s, 40s, 50s, 60s, 70s, and ≥ 80 years) rather than as an exact value, and no other personally identifying information was collected. The clinician surveys (Survey B and Survey C) likewise asked for years of nephrology practice in five ordinal categories (< 5, 5–10, 10–20, 20–30, and ≥ 30 years) and for the monthly volume of hyperkalemia patients in five ordinal categories (none, 1–10, 11–30, 31–100, and ≥ 101 patients), without recording exact counts. All three instruments used a mixture of single-select, multi-select, ranked-choice, and ordinal Likert response formats. In the clinician surveys, ten 5-point Likert items per respondent quantified the importance of maintaining RASi and MRA despite recurrent hyperkalemia, the frequency of three responses to hyperkalemia (dose reduction, discontinuation, and dose maintenance combined with a potassium-lowering agent) for both RASi and MRA, the perceived safety of the non-steroidal MRA relative to spironolactone, and the perceived proportion of chronic hyperkalemia patients who can be controlled by diet alone. Ranked-choice items included the perceived contributors to hyperkalemia (rank up to three), the long-term outpatient management strategy (rank up to two), the limitations of conventional potassium binders (rank up to three), and the unmet needs in long-term hyperkalemia management (rank up to three). The remaining items used single-select categorical formats.

Statistical analysis

Continuous variables derived from decadal categories (patient age via midpoint imputation) are presented as mean (standard deviation [SD]). Ordinal 5-point Likert responses are

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summarized as the mean (95% confidence interval [CI]), with the CI calculated from the t-distribution. All categorical and ranked-choice responses are presented as number (%). Ranked-choice items are reported both as the proportion endorsed as the top-ranked option and as the cumulative proportion endorsed within the top one to three options, with the cumulative endorsements treated analytically as multi-select binary responses.

Where the exposure variable was intrinsically ordered, monotonic trends across the ordered subgroups were tested rather than unstructured between-group differences. In the patient survey, comparisons across the four CKD strata (stage 1–2, stage 3, stage 4, and dialysis-dependent stage 5D) and in the clinician surveys, comparisons across the four monthly hyperkalemia patient-volume strata (none, 1–10, 11–30, and ≥ 31 patients) used the Cochran–Armitage trend test for binary outcomes, the Jonckheere–Terpstra test for ordinal Likert outcomes, and a t-test of the slope from linear regression of the response on group rank for the single continuous variable (patient age). Where the exposure was nominal—namely the two-group comparison of Korean nephrologists with non-nephrology clinicians in the combined Survey B + C dataset—Pearson χ^2 tests were used for binary outcomes, with Fisher's exact tests substituted for 2 × 2 tables in which any expected cell count was below five, and the Mann–Whitney U test was used for ordinal Likert outcomes.

All p-values are two-sided, and a value below 0.05 was considered to indicate statistical significance. No correction for multiple comparisons was applied; the present analyses are descriptive and intended to characterize current KAP rather than to test pre-specified hypotheses. Statistical analyses were performed using R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria), with the base stats package for χ^2, Fisher's exact, and Mann–Whitney U tests, and with the DescTools package for the Cochran–Armitage and Jonckheere–Terpstra trend tests. All figures were generated in Python 3.10.12 using matplotlib version 3.8.

Ethics consideration

The surveys collected no personally identifying information and were administered as anonymous public questionnaires. Before entering the survey, the respondent reviewed an electronic information sheet that described the purpose of the survey, the voluntary nature of participation, the absence of personal data collection, and the intended use of aggregated findings, and then provided online consent to proceed. Survey responses were stored on the respective platform's secured research servers (Korea Gallup for Surveys A and B; Korean Medical Times for Survey C). The study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

Patient survey

Awareness, perception, and management of hyperkalemia

A total of 125 patients with CKD who had been diagnosed with or treated for hyperkalemia completed the survey. Thirty-four respondents (27.2%) were women, and most respondents (97.6%) received care at a tertiary or teaching hospital. Thirty-nine respondents (31.2%) were on maintenance dialysis. By self-reported information, 21 participants (16.8%) were in CKD stage 1–2, 24 (19.2%) in stage 3, 29 (23.2%) in stage 4, and 39 (31.2%) in stage 5D (37 hemodialysis, 2 peritoneal dialysis); 12 patients (9.6%) lacked sufficient information and were excluded from between-group analyses (**Table 1**).

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Table 1. Baseline characteristics and awareness of hyperkalemia among patients with CKD, stratified by self-reported CKD stage (Survey A)

Variable	Total (n = 125)	Stage 1–2 (n = 21)	Stage 3 (n = 24)	Stage 4 (n = 29)	Stage 5D (n = 39)	p-value
Age (yr)	54.8 ± 10.0	61.2 ± 8.0	57.5 ± 10.7	54.0 ± 8.6	50.4 ± 9.4	< 0.001
Female sex	34 (27.2)	13 (61.9)	14 (58.3)	0 (0.0)	3 (7.7)	< 0.001
Awareness of hyperkalemia	114 (91.2)	10 (47.6)	24 (100.0)	29 (100.0)	39 (100.0)	< 0.001
Frequency of being told potassium is high	3.41 (3.30–3.52)	2.95 (2.62–3.29)	3.54 (3.33–3.76)	3.76 (3.52–4.00)	3.36 (3.20–3.52)	0.343
Perceived risk of hyperkalemia	3.97 (3.84–4.10)	2.90 (2.66–3.15)	4.00 (3.82–4.18)	4.45 (4.21–4.69)	4.21 (4.07–4.34)	< 0.001
Culprit cause knowledge: NSAIDs	3.62 (3.48–3.76)	2.62 (2.39–2.85)	3.83 (3.67–3.99)	4.07 (3.87–4.27)	3.82 (3.61–4.03)	< 0.001
Culprit cause knowledge: herbal supplements/ fruit juices	3.56 (3.39–3.73)	3.81 (3.44–4.18)	3.96 (3.64–4.28)	4.00 (3.82–4.18)	2.87 (2.53–3.21)	< 0.001
Culprit cause knowledge: cardiorenal-protective drugs	3.78 (3.64–3.92)	2.86 (2.53–3.19)	4.00 (3.78–4.22)	4.24 (4.02–4.46)	3.97 (3.78–4.16)	< 0.001
Current K-management strategies						
Dietary K restriction	61 (48.8)	1 (4.8)	19 (79.2)	21 (72.4)	14 (35.9)	0.300
Potassium-lowering drug	57 (45.6)	1 (4.8)	14 (58.3)	21 (72.4)	15 (38.5)	0.058
Reduce or stop culprit drugs	18 (14.4)	4 (19.0)	2 (8.3)	5 (17.2)	3 (7.7)	0.349
Most burdensome aspect of hyperkalemia management						
Fear of hyperkalemia complications	41 (32.8)	4 (19.0)	1 (4.2)	21 (72.4)	10 (25.6)	0.082
Dietary restrictions, cooking burden	26 (20.8)	0 (0.0)	11 (45.8)	3 (10.3)	10 (25.6)	0.329
Hospital visits/blood testing burden	31 (24.8)	9 (42.9)	7 (29.2)	0 (0.0)	13 (33.3)	0.327
Drug side effects/inconvenience	20 (16.0)	2 (9.5)	4 (16.7)	5 (17.2)	6 (15.4)	0.627
Preferred hyperkalemia management strategy						
No K-lowering drug + strict low-K diet	39 (31.2)	4 (19.0)	9 (37.5)	11 (37.9)	6 (15.4)	0.464
Daily K-lowering drug + free diet	86 (68.8)	17 (81.0)	15 (62.5)	18 (62.1)	33 (84.6)	0.464
Most frustration with hyperkalemia management						
Inconvenience of taking K-lowering drugs	19 (15.2)	1 (4.8)	6 (25.0)	2 (6.9)	9 (23.1)	0.222
Dietary control difficulty	41 (32.8)	3 (14.3)	13 (54.2)	18 (62.1)	5 (12.8)	0.406
Frequent labs/clinic visits	17 (13.6)	4 (19.0)	2 (8.3)	1 (3.4)	9 (23.1)	0.495
Cost burden	27 (21.6)	1 (4.8)	2 (8.3)	8 (27.6)	11 (28.2)	0.009
Need to reduce/stop other important drugs	11 (8.8)	3 (14.3)	0 (0.0)	0 (0.0)	5 (12.8)	0.764
No particular difficulties	10 (8.0)	9 (42.9)	1 (4.2)	0 (0.0)	0 (0.0)	< 0.001

Values are presented as number (%), mean ± standard deviation or median (minimum–maximum).
Trend across the four ordered CKD strata (stage 1–2, stage 3, stage 4, stage 5D) was tested with the Cochran–Armitage trend test for binary outcomes and the Jonckheere–Terpstra trend test for ordinal Likert outcomes; the slope from linear regression of the response on group rank was tested with a t-test for the continuous variable age.
CKD, chronic kidney disease; NSAID, non-steroidal anti-inflammatory drug; Stage 5D, dialysis-dependent stage 5 chronic kidney disease.

Awareness of hyperkalemia was high, with 114 patients (91.2%) reporting prior knowledge of the term, which increased monotonically across CKD stages (p = 0.001): every patient in stages 3, 4, and 5D was familiar with the term, whereas only 47.6% of those in stages 1–2 were. The perceived risk of hyperkalemia increased significantly with stage (p = 0.001), from 2.90 (95% CI, 2.66–3.15) in stage 1–2 to 4.45 (95% CI, 4.21–4.69) in stage 4 and 4.21 (95% CI, 4.07–4.34) in stage 5D. Recognition that cardio-kidney-protective drugs (RASi/MRA) and non-steroidal anti-inflammatory drugs (NSAIDs) contribute to hyperkalemia also increased monotonically across stages (RASi/MRA: 2.86 [2.53–3.19] in stage 1–2 versus 4.24 [4.02–4.46] in stage 4, p < 0.001; NSAIDs: 2.62 [2.39–2.85] versus 4.07 [3.87–4.27], p = 0.001).

Among current management practices, dietary education was the most common (48.8%), followed by potassium-lowering pharmacotherapy (45.6%); reduction or discontinuation of culprit medications was infrequent (14.4%; p = 0.349). The most frequently selected single burden of hyperkalemia care was fear of acute potassium-related emergencies (32.8%). Overall satisfaction with hyperkalemia care was 3.59 (3.46–3.72) and increased monotonically with stage (p = 0.002).

Experience of hyperkalemia management

Sixty-four respondents (51.2%) reported current or prior use of RASi or MRA and formed the

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analytic subgroup. The two most commonly endorsed clinician responses to a hyperkalemic episode were reduction of the culprit drug with low-potassium dietary counseling (42.2%) and maintenance of the existing dose with addition of a potassium-lowering agent (42.2%); only 3 patients (4.7%) reported complete discontinuation. Dose reduction without addition of a potassium-lowering agent clustered in stage 3 (15/16, 93.8%), whereas the dose-maintenance strategy with a potassium-lowering agent was more common in stages 4 (62.1%) and 5D (50.0%) (p = 0.011 and 0.113, respectively). When asked how they felt about dose reduction or discontinuation of cardio-kidney-protective therapy, 26 (40.6%) preferred to continue the original drug even if a potassium-lowering agent had to be added, 25 (39.1%) were concerned that withdrawal would worsen cardio-kidney outcomes, and only 13 (20.3%) felt reassured by drug withdrawal. The proportion of patients worried about cardio-kidney deterioration decreased monotonically with stage (p = 0.009) (**Table 2**).

Nephrology expert survey

Practice profile and perception of hyperkalemia causes

A total of 82 nephrologists, all members of the KSN, completed the survey; tertiary or teaching hospitals were the most common practice setting (40.2%), and the mean duration of nephrology practice was 15.7 years (SD, 10.9). Respondents were stratified by self-reported monthly hyperkalemia patient volume into four groups (none, 1–10, 11–30, ≥ 31 patients): 6 (7.3%), 16 (19.5%), 17 (20.7%), and 43 (52.4%), respectively. The serum potassium threshold for active intervention was 5.5–5.9 mEq/L in 45 (54.9%), 5.0–5.4 in 23 (28.0%), and ≥ 6.0 in 14 (17.0%). Among the top three causes of chronic hyperkalemia, CKD was the most commonly endorsed (86.6%), followed by excessive dietary potassium intake (50.0%), RASi (42.7%), MRA (31.7%), and NSAIDs (25.6%). Endorsement of MRA as a top-three cause increased monotonically across patient-volume strata (0% versus 41.9%, p = 0.007).

Hyperkalemia management

Perceptions of RASi and MRA management are summarized in **Fig. 1**. The overall mean importance of RASi maintenance was 4.06 (3.91–4.22) and increased monotonically across patient-volume strata (3.67 [2.81–4.52] versus 4.23 [4.04–4.42] in the ≥ 31 group; p = 0.023;

Table 2. Experience of cardiorenal-protective therapy (RASi or MRA) in the patient subgroup who had used these agents (Survey A), stratified by self-reported CKD stage

Variable	Total (n = 64)	Stage 1–2 (n = 2)	Stage 3 (n = 16)	Stage 4 (n = 29)	Stage 5D (n = 12)	p-value
The clinician's strategy when hyperkalemia occurred						
Maintain RASi/MRA dose + low-K diet education	6 (9.4)	0 (0.0)	0 (0.0)	3 (10.3)	0 (0.0)	0.754
Reduce RASi/MRA dose + low-K diet education	27 (42.2)	0 (0.0)	15 (93.8)	7 (24.1)	4 (33.3)	0.011
Stop temporarily/permanently RASi/MRA + low-K diet education	3 (4.7)	0 (0.0)	0 (0.0)	1 (3.4)	1 (8.3)	0.235
Maintain RASi/MRA dose + add K-lowering drug	27 (42.2)	2 (100.0)	1 (6.2)	18 (62.1)	6 (50.0)	0.113
Reduce RASi/MRA dose + add K-lowering drug	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0.137
Stop RASi/MRA + add K-lowering drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Reduce RASi/MRA only	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Stop temporarily/permanently RASi/MRA only	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Emotional response to culprit drug reduction						
Relieved: high K is fatal, stopping helps lower it	13 (20.3)	0 (0.0)	1 (6.2)	6 (20.7)	3 (25.0)	0.130
Worried: kidney/heart will worsen without the drug	25 (39.1)	2 (100.0)	12 (75.0)	6 (20.7)	5 (41.7)	0.009
Prefer to keep the drug even if K-binder is added	26 (40.6)	0 (0.0)	3 (18.8)	17 (58.6)	4 (33.3)	0.143

Values are presented as number (%).
Reported clinician response to a hyperkalemic episode, patient emotional response, and preference for continued therapy were compared across the four ordered CKD strata. The trend across strata was tested using the Cochran–Armitage trend test.
CKD, chronic kidney disease; K-binder, potassium binder; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; Stage 5D, dialysis-dependent stage 5 chronic kidney disease.

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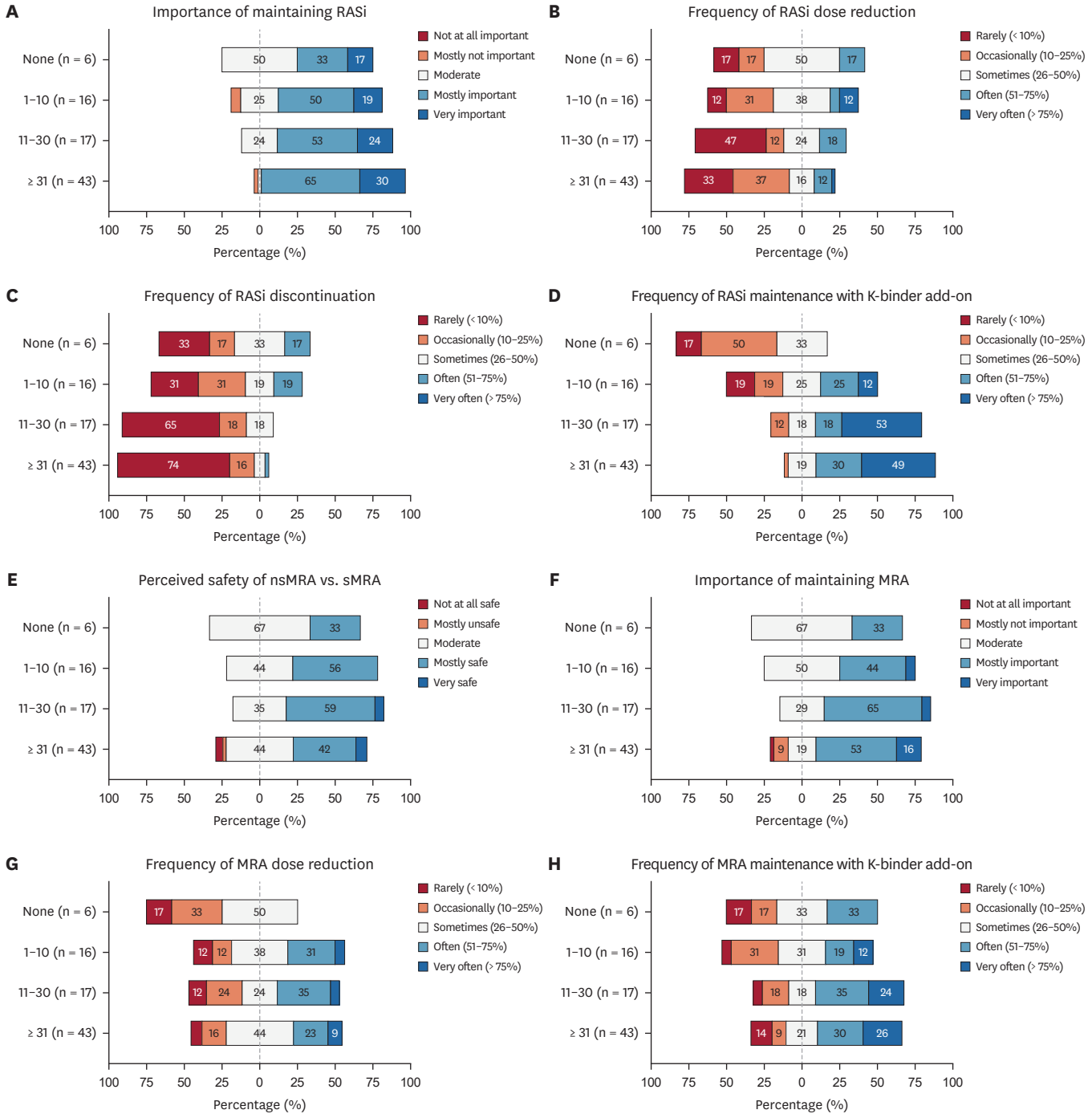

Fig. 1. Self-reported perception and behavior regarding RASi and MRA management among Nephrologists (Survey B, n = 82), stratified by self-reported monthly hyperkalemia patient volume (none, 1–10, 11–30, ≥ 31 patients per month). Each panel shows a diverging stacked-bar Likert plot: negative responses (1–2) extend to the left, the neutral midpoint (3) is centered on zero, and positive responses (4–5) extend to the right. Subgroup sample sizes are shown next to each y-axis label. (A) Importance of maintaining RASi; (B) Frequency of RASi dose reduction; (C) Frequency of RASi discontinuation; (D) Frequency of RASi maintenance with K-binder add-on; (E) Perceived safety of nsMRA vs. sMRA; (F) Importance of maintaining MRA; (G) Frequency of MRA dose reduction; (H) Frequency of MRA maintenance with K-binder add-on.
K-binder, potassium binder; MRA, mineralocorticoid receptor antagonist; nsMRA, non-steroidal mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; sMRA, steroidal mineralocorticoid receptor antagonist.

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Fig. 1A). When hyperkalemia occurred during RASi therapy, the most frequent action was to maintain the dose and add a potassium binder (mean frequency 3.82 [3.55–4.08]); this strategy was reported more often as patient volume increased (2.17 [1.38–2.96] versus 4.26 [3.99–4.52], $p < 0.001$; **Fig. 1D**). Full RASi discontinuation was infrequent overall (1.65 [1.44–1.85]) and decreased monotonically ($p = 0.003$; **Fig. 1C**). For MRAs, the perceived safety of non-steroidal mineralocorticoid receptor antagonist (nsMRA) versus steroidal mineralocorticoid receptor antagonist (sMRA) was 3.51 (3.35–3.67) (**Fig. 1E**), and the importance of maintaining MRA was 3.67 (3.50–3.84) (**Fig. 1F**). When hyperkalemia occurred during MRA therapy, dose reduction (3.02 [2.79–3.26]) was the most frequent action, followed by maintenance with binder add-on (3.33 [3.05–3.61]); none of these strategies showed a significant linear trend (**Fig. 1G and H**).

For long-term outpatient management, the strategies most commonly endorsed within the top two ranks were potassium-binder prescription (75.6%) and dietary education (69.5%), both increasing monotonically with patient volume (binder 33.3% versus 93.0%, $p < 0.001$; diet 50.0% versus 83.7%, $p = 0.005$), whereas endorsement of reducing or stopping culprit drugs decreased (50.0% versus 9.3%, $p < 0.001$). Among limitations of existing CPS/SPS binders, constipation (80.5%) and taste, odor, or powder discomfort (69.5%) were the most frequently endorsed within the top three ranks. For newer potassium binders (SZC and patiromer), respondents most often identified faster and more predictable potassium reduction as the top advantage (32.9%); the most frequently selected single barrier was non-reimbursement with consequent cost burden (73.2%).

Physician survey

Practice profile and perception of hyperkalemia causes

A total of 255 multispecialty physicians completed the survey. The largest specialty groups were general internal medicine (26.7%), family medicine (14.5%), nephrology (11.0%), endocrinology (5.9%), cardiology (4.7%), and emergency medicine (4.3%); local clinics were the most common practice setting (36.5%). When stratified by monthly hyperkalemia patient volume, 27 (10.6%), 159 (62.4%), 42 (16.5%), and 27 (10.6%) respondents reported none, 1–10, 11–30, and ≥ 31 patients, respectively. The serum potassium threshold for intervention was 5.5–5.9 mEq/L in 136 (53.3%) and 5.0–5.4 in 49 (19.2%). Among the top three causes endorsed, CKD was again the most common (84.7%), followed by RASi (39.6%), MRA (34.1%), diabetes mellitus (29.8%), and metabolic acidosis (28.6%); MRA endorsement increased monotonically with patient volume (29.6% versus 55.6%, $p = 0.006$).

Hyperkalemia management

The perception and behavior patterns of physicians regarding RASi and MRA management are shown in **Fig. 2**. The mean importance of maintaining RASi was 3.73 (3.62–3.83), lower than the corresponding figure in Survey B, and rose monotonically with patient volume ($p = 0.003$; **Fig. 2A**). The frequency of maintaining the RASi dose with the addition of a potassium binder (2.94 [2.79–3.08]) also increased monotonically (2.59 versus 3.78, $p < 0.001$; **Fig. 2D**). For MRAs, dose reduction (3.25 [3.12–3.39]) was the most frequent action, and both dose reduction and maintenance with binder add-on increased in the ≥ 31 group ($p = 0.049$ and 0.033; **Fig. 2G and H**). A specialty-stratified analysis of the nine 5-point items in Survey C across the seven primary-specialty groups (nephrology, cardiology, endocrinology, general internal medicine, family medicine, emergency medicine, and other; **Supplementary Fig. 1**) showed that inter-specialty differences within the multispecialty physician cohort were concentrated in items related to maintaining RASi or MRA therapy and combining it

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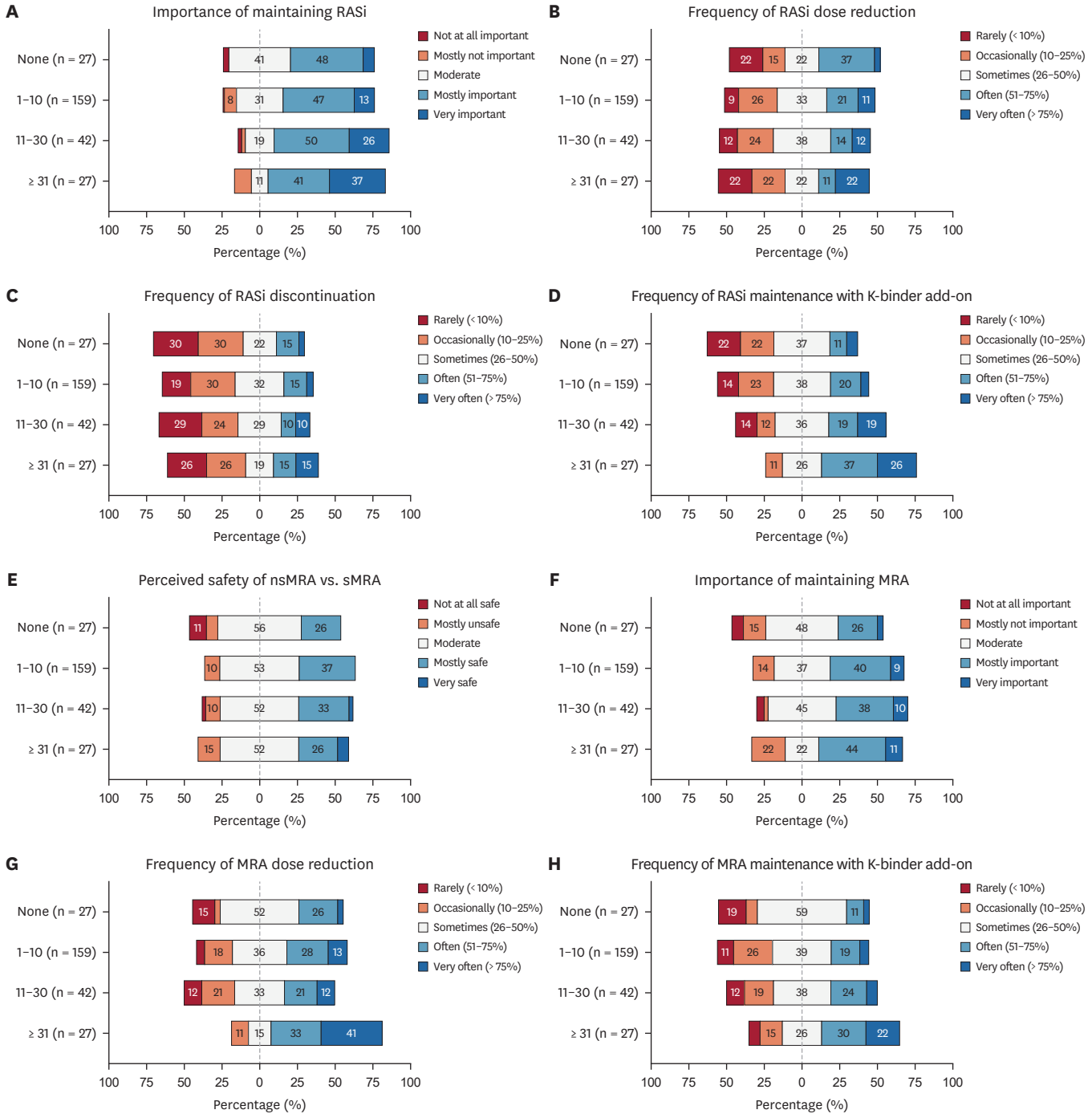

Fig. 2. Self-reported perception and behavior regarding RASi and MRA management among Korean Medical Association members (Survey C, n = 255), stratified by self-reported monthly hyperkalemia patient volume. Each panel shows a diverging stacked-bar Likert plot: negative responses (1–2) extend to the left, the neutral midpoint (3) is centered on zero, and positive responses (4–5) extend to the right. Subgroup sample sizes are shown next to each y-axis label.
(A) Importance of maintaining RASi; (B) Frequency of RASi dose reduction; (C) Frequency of RASi discontinuation; (D) Frequency of RASi maintenance with K-binder add-on; (E) Perceived safety of nsMRA vs. sMRA; (F) Importance of maintaining MRA; (G) Frequency of MRA dose reduction; (H) Frequency of MRA maintenance with K-binder add-on.
K-binder, potassium binder; MRA, mineralocorticoid receptor antagonist; nsMRA, non-steroidal mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; sMRA, steroidal mineralocorticoid receptor antagonist.

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with a potassium binder (p = 0.048 for the importance of maintaining RASi, p = 0.003 for RASi maintenance plus binder add-on, p = 0.004 for the importance of maintaining MRA, and p = 0.022 for MRA maintenance plus binder add-on).

For long-term outpatient management, the two strategies most often endorsed within the top two ranks were dietary education (60.4%) and reduction or discontinuation of culprit drugs (57.3%), whereas prescription of a potassium binder was less common (29.4%). Among the limitations of CPS/SPS binders, the most frequently endorsed were taste/odor discomfort (57.6%), constipation (52.5%), drug interactions or separation-of-dosing burden (43.9%), and limited prescribing experience (20.8%). For newer potassium binders, respondents most often selected selective potassium absorption as the top advantage (32.9%).

Combined comparison

Nephrology versus non-nephrology clinicians

Survey B respondents (n = 82) were merged with the Survey C nephrology subset (n = 28) to form a Nephrology group (n = 110); the remaining Survey C respondents formed the Non-nephrologist group (n = 227). Results are presented in **Table 3**. Nephrologists rated the importance of maintaining RASi higher than non-nephrologists (4.10 [3.96–4.24] versus 3.67 [3.55–3.78], p < 0.001) and reported maintaining the RASi dose with the addition of a potassium binder more frequently (3.79 [3.57–4.01] versus 2.84 [2.69–2.99], p < 0.001). Nephrologists reported reducing the RASi dose less often (2.46 versus 2.95, p < 0.001) and discontinuing RASi less often (1.84 versus 2.56, p < 0.001). For MRAs, nephrologists rated nsMRA as safer than sMRA (3.45 versus 3.22, p = 0.007), rated maintaining MRA as more important (3.64 versus 3.38, p = 0.006), and reported maintenance with binder add-on more frequently (3.37 versus 2.83, p < 0.001); MRA discontinuation differed modestly (2.51 versus 2.73, p = 0.037) and the frequency of dose reduction did not differ (p = 0.708).

The two groups also diverged in priorities for long-term outpatient management. Among the strategies endorsed within the top two ranks, potassium-binder prescription was chosen by 68.2% of nephrologists versus 27.3% of non-nephrologists (p < 0.001), whereas reduction or discontinuation of culprit drugs was chosen by 35.5% versus 55.5% (p < 0.001). Non-nephrologists more often endorsed limited prescribing experience as a binder limitation (22.5% versus 2.7%, p < 0.001) and difficulty in maintaining RASi or MRA long-term as an unmet need (57.3% versus 18.2%, p < 0.001), whereas nephrologists more often endorsed low adherence to existing binders (61.8% versus 29.1%, p < 0.001) and cost or insurance burden (46.4% versus 19.4%, p < 0.001).

DISCUSSION

In this nationwide descriptive cross-sectional study, we characterized contemporary KAP regarding hyperkalemia management among three Korean stakeholder groups—patients with kidney-related diagnoses and prior hyperkalemia care, nephrology specialists, and a multispecialty physician cohort—against the backdrop of expanding use of RASi, MRA, and high-potency potassium binders. To our knowledge, this is the first survey to bring these three stakeholder groups together within a single national context. The parallel design enabled direct comparison between patient-side perception and clinician-side practice, and between Korean nephrologists and non-nephrology clinicians—two contrasts that the existing literature has not systematically addressed. By aligning the data collection with the

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Table 3. Comparison of clinician perspectives on hyperkalemia management between Korean nephrologists (combined Survey B and Survey C nephrology subset) and non-nephrology clinicians (Survey C non-nephrology subset)

Variable	Total (n = 337)	Nephrologists (n = 110)	Non-nephrologists (n = 227)	p-value
RASi management in patients with hyperkalemia				
Importance of maintaining RASi despite recurrent hyperkalemia	3.81 (3.72–3.90)	4.10 (3.96–4.24)	3.67 (3.55–3.78)	< 0.001
Frequency: reduce RASi dose	2.79 (2.66–2.92)	2.46 (2.24–2.69)	2.95 (2.79–3.10)	< 0.001
Frequency: discontinue RASi	2.32 (2.19–2.45)	1.84 (1.64–2.04)	2.56 (2.40–2.71)	< 0.001
Frequency: maintain RASi + add potassium binder	3.15 (3.02–3.28)	3.79 (3.57–4.01)	2.84 (2.69–2.99)	< 0.001
MRA management in patients with hyperkalemia				
Perceived safety of nsMRA vs. sMRA	3.30 (3.22–3.38)	3.45 (3.31–3.60)	3.22 (3.13–3.32)	0.007
Importance of maintaining MRA despite recurrent hyperkalemia	3.47 (3.37–3.56)	3.64 (3.47–3.80)	3.38 (3.27–3.49)	0.006
Frequency: reduce MRA dose	3.20 (3.08–3.32)	3.16 (2.95–3.37)	3.22 (3.07–3.36)	0.708
Frequency: discontinue MRA	2.66 (2.54–2.78)	2.51 (2.29–2.73)	2.73 (2.59–2.87)	0.037
Frequency: maintain MRA + add potassium binder	3.01 (2.89–3.13)	3.37 (3.14–3.60)	2.83 (2.69–2.97)	< 0.001
Long-term outpatient strategy (multiple choices up to 2)				
Dietary education	211 (62.6)	68 (61.8)	143 (63.0)	0.929
Reduce/stop culprit drugs (RASi/MRA)	165 (49.0)	39 (35.5)	126 (55.5)	< 0.001
Add/up-titrate diuretics	60 (17.8)	11 (10.0)	49 (21.6)	0.014
Prescribe potassium binder	137 (40.7)	75 (68.2)	62 (27.3)	< 0.001
Shorten potassium monitoring interval	67 (19.9)	22 (20.0)	45 (19.8)	1.000
Is diet alone sufficient for stable K control				
Proportion of chronic hyperkalemia patients	2.61 (2.53–2.70)	2.65 (2.50–2.79)	2.60 (2.49–2.71)	0.847
Limitations of existing potassium binders (multiple choices up to 3)				
Taste/odor discomfort	204 (60.5)	78 (70.9)	126 (55.5)	0.009
Constipation	200 (59.3)	91 (82.7)	109 (48.0)	< 0.001
GI side effects other than constipation	126 (37.4)	38 (34.5)	88 (38.8)	0.528
Reduced long-term adherence	145 (43.0)	60 (54.5)	85 (37.4)	0.004
Unsatisfactory K-lowering effect	80 (23.7)	17 (15.5)	63 (27.8)	0.019
Drug interactions + separation timing burden	132 (39.2)	29 (26.4)	103 (45.4)	0.001
Cost burden	18 (5.3)	2 (1.8)	16 (7.0)	0.081
Limited prescribing experience	54 (16.0)	3 (2.7)	51 (22.5)	< 0.001
Unmet needs in hyperkalemia management (multiple choices up to 3)				
Diet alone is insufficient	198 (58.8)	51 (46.4)	147 (64.8)	0.002
Difficulty maintaining RASi/MRA long-term	150 (44.5)	20 (18.2)	130 (57.3)	< 0.001
Poor convenience of existing binders	160 (47.5)	46 (41.8)	114 (50.2)	0.183
GI side effects of existing binders	121 (35.9)	53 (48.2)	68 (30.0)	0.002
Low adherence to existing binders	134 (39.8)	68 (61.8)	66 (29.1)	< 0.001
Cost/insurance burden	95 (28.2)	51 (46.4)	44 (19.4)	< 0.001
Burden of continual hyperkalemia monitoring	88 (26.1)	22 (20.0)	66 (29.1)	0.100

Five-point Likert items are summarized as mean (95% CI) and compared with the Mann–Whitney U test; binary categorical items are summarized as number (%) and compared with the Pearson χ^2 test, or with the Fisher's exact test for 2 × 2 tables in which any expected cell count was below five. All p-values are two-sided. GI, gastrointestinal; MRA, mineralocorticoid receptor antagonist; nsMRA, non-steroidal mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; sMRA, steroidal mineralocorticoid receptor antagonist.

2024 KDIGO CKD guideline and the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America heart failure guideline [13,14], the present study provides a contemporary snapshot of how the shift toward preserving cardio-kidney-protective therapy has been received by both patients and clinicians in routine Korean practice.

In this study, patient awareness of hyperkalemia and its clinical consequences was high. Self-reported familiarity with the term reached 91.2%; the overall perceived risk of hyperkalemia was 3.97 (95% CI, 3.84–4.10) on a five-point scale; and risk perception increased monotonically across CKD stages. Recognition that cardio-kidney-protective drugs such as RASi and MRA can raise serum potassium was also relatively high at 3.78 (3.64–3.92), again with a monotonic increase across CKD stages. Despite this elevated awareness, only 18 patients (14.4%) selected reduction or discontinuation of the culprit drug as their preferred response to a hyperkalemic episode, whereas dietary education (48.8%) and potassium-lowering pharmacotherapy (45.6%) were chosen more often. Among the

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subgroup who had used RASi or MRA, 40.6% expressed a preference to continue the original drug even if a potassium-lowering agent had to be added, and 39.1% reported concern that withdrawal would worsen cardio-kidney outcomes. This pattern is consistent with the direction of recent guideline updates, which favor maintenance of cardio-kidney-protective therapy whenever potassium can be controlled by other means [13,14].

Our findings extend and partly diverge from previous patient-facing works [22]. The Japanese cohort described by Shibagaki et al. [23] and Sada et al. [24] reported high self-reported adherence to potassium binders and perceived less impact on quality of life from binder therapy than from dietary restriction, supporting the view that pharmacologic potassium control is acceptable to patients managing multiple lifestyle limitations. In contrast, a Saudi Arabian survey reported that 79.7% of CKD patients had inadequate knowledge of potassium-rich foods [25], and a United States cohort showed that knowledge of dietary restrictions did not translate into measured potassium intake [26]. The Korean respondents in our study, therefore, appeared to combine relatively high disease-specific knowledge with an explicit willingness to preserve cardio-kidney-protective therapy, even at the cost of accepting additional medication. The greater representation of tertiary-hospital-treated and advanced-CKD patients in our sample may have contributed to this profile and should be considered when generalizing the findings to less-specialized care settings.

Both clinician surveys identified CKD as the most frequently endorsed cause of chronic hyperkalemia, followed by excessive dietary potassium intake, renin–angiotensin system blockers, and MRA. The importance of maintaining RASi and MRA despite recurrent hyperkalemia was rated 3.81 (3.72–3.90) and 3.47 (3.37–3.56), respectively, on the combined five-point scale, indicating broad recognition of these agents' cardio-kidney-protective role across specialties. Nephrologists, however, rated maintenance as more important than non-nephrology clinicians for both drug classes ($p < 0.001$ for RASi, $p = 0.006$ for MRA).

This specialty gradient extended to reported management practices when hyperkalemia developed during ongoing therapy. For RASi, nephrologists reported dose reduction less often (mean 2.46 [2.24–2.69] versus 2.95 [2.79–3.10], $p < 0.001$), drug discontinuation less often (1.84 [1.64–2.04] versus 2.56 [2.40–2.71], $p < 0.001$), and dose maintenance with addition of a potassium binder more often (3.79 [3.57–4.01] versus 2.84 [2.69–2.99], $p < 0.001$) than non-nephrology clinicians. For MRA, nephrologists similarly reported dose maintenance with potassium-binder add-on more often (3.37 [3.14–3.60] versus 2.83 [2.69–2.97], $p < 0.001$) and discontinuation less often (2.51 [2.29–2.73] versus 2.73 [2.59–2.87], $p = 0.037$), whereas the frequency of dose reduction did not differ between groups ($p = 0.708$). These contrasts mirror those described in the Gulf Cooperation Council survey [27], the Spanish national multispecialty survey [28], the European Society of Cardiology Heart Failure Association survey [29], the nationwide Swedish survey [30], and the UK-based cardio-kidney perspective [31], all of which reported wide inter-specialty variation in dose reduction, discontinuation, and binder add-on once hyperkalemia developed.

The two clinician groups also diverged in their priorities for long-term outpatient management. Among the top two strategies endorsed for chronic outpatient hyperkalemia, nephrologists most often selected prescription of a potassium binder (68.2%) and dietary education (61.8%), whereas non-nephrology clinicians most often selected dietary education (63.0%) and reduction or discontinuation of culprit drugs (55.5%). The two groups held comparably neutral views on whether diet alone was sufficient for stable potassium control

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(2.65 [2.50–2.79] in the Nephrology group versus 2.60 [2.49–2.71] in the Non-nephrology group, p = 0.847), so the divergent strategy preferences appear to reflect different attitudes toward the active use of potassium-binding agents rather than different perceptions of dietary feasibility. The disproportionate endorsement of limited prescribing experience as a binder limitation among non-nephrology respondents (22.5% versus 2.7%, p < 0.001) suggests that lower familiarity with the newer potassium binders, rather than a different assessment of the clinical role of these agents, is a major contributor to the specialty gap in outpatient strategy [32-34].

This study has several limitations. First, the patient survey was distributed through a kidney disease patient community on the web-based platform rather than to consecutive clinic attendees, an approach that carries a recognized risk of fraudulent respondents [21]. To mitigate this risk, eligibility was first verified through screening items on hyperkalemia diagnosis and prior treatment history; each respondent additionally provided the name of the treating institution and the attending clinician, and a small set of follow-up items required knowledge consistent with actual hyperkalemia care. Responses with internally inconsistent or implausible entries were removed during data cleaning. Second, the clinician surveys were also web-based and did not collect any identifying information, leaving a residual possibility of duplicate or non-physician responses. Distribution was nevertheless restricted to the membership channels of trusted national societies, which provided intrinsic verification of professional status. Third, the patient sample was concentrated in tertiary or teaching hospitals (97.6%), which may not reflect the experiences of patients followed exclusively in primary or secondary care. Patients managed in primary or secondary care settings, whose access to up-to-date hyperkalemia education and to specialist-led prescribing of newer potassium binders may be more limited, are therefore under-represented in our data; the patient-side awareness and preference profiles reported here may overestimate those typically seen outside tertiary care, and targeted educational outreach at primary and secondary care levels may be needed to close this gap. Fourth, the cross-sectional design captured stated attitudes and intended management rather than observed prescribing or clinical outcomes; the specialty contrasts reported here therefore reflect differences in self-reported preference rather than measured behavior. Additionally, the present analyses were exploratory and descriptive: p-values were two-sided and were not adjusted for multiple comparisons, and the absence of a pre-specified hypothesis precludes causal inference. Finally, because the combined Nephrology group pooled respondents recruited through two different channels (Survey B via the KSN listserv, n = 82; Survey C nephrology subset via the Korean Medical Times portal, n = 28), a sensitivity comparison of the two sub-cohorts was performed; the distribution of practice setting did not differ significantly between them (p = 0.394; **Supplementary Table 2**), supporting the validity of the pooled analysis.

Patients with kidney-related diagnoses and prior hyperkalemia care showed both high awareness of hyperkalemia and a clear preference for maintaining cardio-kidney-protective therapy. Nephrologists and physicians outside nephrology rated the importance of maintaining RASi and MRA similarly highly, but the practical translation of this view diverged. Lower monthly patient volume with hyperkalemia and non-nephrology specialty were each associated with a greater willingness to reduce or discontinue these agents rather than combine them with a potassium binder. Together, these findings indicate a contemporary practice gap between the direction of recent guidelines and real-world clinician behavior outside nephrology, despite broadly shared recognition of the rationale for preserving cardio-kidney-protective therapy.

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Conclusion

In a nationwide Korean survey covering patients, nephrologists, and a multispecialty physician cohort, awareness of hyperkalemia and of the contribution of cardio-kidney-protective drugs to elevated potassium was high across stakeholder groups, but the willingness to maintain RASi and MRA therapy while controlling potassium pharmacologically was substantially greater among nephrologists than among other specialties. Continued cross-specialty educational outreach on contemporary guideline recommendations for managing hyperkalemia in the setting of cardio-kidney-protective therapy may be particularly valuable for non-nephrology clinicians who manage CKD and heart failure outside specialist clinics. Future studies linking self-reported attitudes to actual prescribing patterns and to longitudinal patient outcomes will be needed to determine whether closing this specialty gap translates into improved cardio-kidney preservation.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

CHERRIES compliance

Supplementary Table 2

Sensitivity comparison of the two nephrologist sub-cohorts that were pooled to form the Nephrology group used in the main **Table 3** (n = 110 in the manuscript)

Supplementary Fig. 1

Self-reported perception and behavior regarding RASi and MRA management among Korean Medical Association members (Survey C, n = 255), stratified by self-reported clinical specialty (nephrology, cardiology, endocrinology, general internal medicine, family medicine, emergency department, and other).

REFERENCES

1. Kovesdy CP. Management of hyperkalaemia in chronic kidney disease. *Nat Rev Nephrol* 2014;10:653-662. PUBMED | CROSSREF
2. Kovesdy CP, Appel LJ, Grams ME, et al. Potassium homeostasis in health and disease: a scientific workshop cosponsored by the National Kidney Foundation and the American Society of Hypertension. *Am J Kidney Dis* 2017;70:844-858. PUBMED | CROSSREF
3. Khanagavi J, Gupta T, Aronow WS, et al. Hyperkalemia among hospitalized patients and association between duration of hyperkalemia and outcomes. *Arch Med Sci* 2014;10:251-257. PUBMED | CROSSREF
4. Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. *N Engl J Med* 2004;351:585-592. PUBMED | CROSSREF
5. Kashihara N, Kohsaka S, Kanda E, Okami S, Yajima T. Hyperkalemia in real-world patients under continuous medical care in Japan. *Kidney Int Rep* 2019;4:1248-1260. PUBMED | CROSSREF
6. Rossignol P, Lainscak M, Crespo-Leiro MG, et al. Unravelling the interplay between hyperkalaemia, renin-angiotensin-aldosterone inhibitor use and clinical outcomes. Data from 9222 chronic heart failure patients of the ESC-HFA-EORP Heart Failure Long-Term Registry. *Eur J Heart Fail* 2020;22:1378-1389. PUBMED | CROSSREF
7. Cho IJ, Kang SM. Angiotensin receptor-neprilysin inhibitor in patients with heart failure and chronic kidney disease. *Kidney Res Clin Pract* 2021;40:555-565. PUBMED | CROSSREF
8. Kanda E, Rastogi A, Murohara T, et al. Clinical impact of suboptimal RAASi therapy following an episode of hyperkalemia. *BMC Nephrol* 2023;24:18. PUBMED | CROSSREF

https://doi.org/10.5049/EBP.2026.24.e9

9. Volterrani M, Perrone V, Sangiorgi D, et al. Effects of hyperkalaemia and non-adherence to renin-angiotensin-aldosterone system inhibitor therapy in patients with heart failure in Italy: a propensity-matched study. *Eur J Heart Fail* 2020;22:2049-2055. PUBMED | CROSSREF
10. Polson M, Lord TC, Kangethe A, et al. Clinical and economic impact of hyperkalemia in patients with chronic kidney disease and heart failure. *J Manag Care Spec Pharm* 2017;23:S2-S9. PUBMED | CROSSREF
11. Clase CM, Carrero JJ, Ellison DH, et al. Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2020;97:42-61. PUBMED | CROSSREF
12. Sterns RH, Rojas M, Bernstein P, Chennupati S. Ion-exchange resins for the treatment of hyperkalemia: are they safe and effective? *J Am Soc Nephrol* 2010;21:733-735. PUBMED | CROSSREF
13. Stevens PE, Ahmed SB, Carrero JJ, et al. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2024;105:S117-S314. PUBMED | CROSSREF
14. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure. *Circulation* 2022;145:e895-e1032. PUBMED | CROSSREF
15. Cha DR. Mineralocorticoid receptor blockade for renoprotection. *Kidney Res Clin Pract* 2018;37:183-184. PUBMED | CROSSREF
16. Spinowitz BS, Fishbane S, Pergola PE, et al. Sodium zirconium cyclosilicate among individuals with hyperkalemia: a 12-month phase 3 study. *Clin J Am Soc Nephrol* 2019;14:798-809. PUBMED | CROSSREF
17. Weir MR, Bakris GL, Bushinsky DA, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med* 2015;372:211-221. PUBMED | CROSSREF
18. Rastogi A, Pollack CV Jr, Sánchez Lázaro IJ, et al. Maintained renin-angiotensin-aldosterone system inhibitor therapy with sodium zirconium cyclosilicate following a hyperkalaemia episode: a multicountry cohort study. *Clin Kidney J* 2024;17:sfae083. PUBMED | CROSSREF
19. Eysenbach G. Improving the quality of web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). *J Med Internet Res* 2004;6:e34. PUBMED | CROSSREF
20. Baffour S, Löwe B, Braun A, Uhlenbusch N. Optimizing recruitment in rare disease research: a cross-sectional online study evaluating sampling strategies for hard-to-reach populations. *Orphanet J Rare Dis* 2026;21:29. PUBMED | CROSSREF
21. Pratt-Chapman M, Moses J, Arem H. Strategies for the identification and prevention of survey fraud: data analysis of a web-based survey. *JMIR Cancer* 2021;7:e30730. PUBMED | CROSSREF
22. Grandy S, Jackson J, Moon R, Bluff D, Palaka E. Health-related quality of life and lifestyle changes in patients with chronic kidney disease and hyperkalaemia: real-world data from the US, five European countries and China. *Int J Clin Pract* 2021;75:e14326. PUBMED | CROSSREF
23. Shibagaki Y, Yamazaki H, Wakita T, et al. Impact of treatment of hyperkalaemia on quality of life: design of a prospective observational cohort study of long-term management of hyperkalaemia in patients with chronic kidney disease or chronic heart failure in Japan. *BMJ Open* 2023;13:e074090. PUBMED | CROSSREF
24. Sada K, Yamazaki H, Wakita T, et al. Quality of life in hyperkalemia: baseline analysis of a cohort study of management of hyperkalemia in patients with chronic kidney disease or heart failure in Japan. *medRxiv*. 2026 Mar 25. https://doi.org/10.64898/2026.03.24.26349144. CROSSREF
25. Somaili M, Hakami A, Madkhali J, et al. Cross-sectional study for assessment of knowledge, attitudes and practices of chronic kidney disease patients in Saudi Arabia. *Medicine (Baltimore)* 2025;104:e42260. PUBMED | CROSSREF
26. Betz M, Steenes A, Peterson L, Saunders M. Knowledge does not correspond to adherence of renal diet restrictions in patients with chronic kidney disease stage 3-5. *J Ren Nutr* 2021;31:351-360. PUBMED | CROSSREF
27. AlSahow A, AbdulShafy M, Al-Ghamdi S, et al. Prevalence and management of hyperkalemia in chronic kidney disease and heart failure patients in the Gulf Cooperation Council (GCC). *J Clin Hypertens (Greenwich)* 2023;25:251-258. PUBMED | CROSSREF
28. Diez A, Fernandez N, Garcia M, et al. Insights into the adoption of consensus guidelines for hyperkalemia management in Spain: a national, multicenter, descriptive analysis. *Nephrol Dial Transplant* 2025;40:gfaf116.1556. CROSSREF
29. Christodorescu R, Geavlete O, Ferrini M, et al. Translating the 2021 ESC heart failure guideline recommendations in daily practice: results from a Heart Failure Association survey. *Eur J Heart Fail* 2025;27:412-420. PUBMED | CROSSREF
30. Ferrannini G, Biber ME, Abdi S, Ståhlberg M, Lund LH, Savarese G. The management of heart failure in Sweden-the physician's perspective: a survey. *Front Cardiovasc Med* 2024;11:1385281. PUBMED | CROSSREF
31. Kalsi N, Birkhoelzer S, Kalra PA, Kalra PR. Impact of hyperkalaemia in managing cardiorenal patients — a healthcare professional perspective. *Br J Cardiol* 2018;25:97-101. CROSSREF

32. Wheeler DC, Søndergaard H, Gwynn C, et al. Randomised, blinded, cross-over evaluation of the palatability of and preference for different potassium binders in participants with chronic hyperkalaemia in the USA, Canada and Europe: the APPETIZE study. *BMJ Open* 2024;14:e074954. PUBMED | CROSSREF

33. Han S, Kim S. A new era in diabetic kidney disease treatment: the four pillars and strategies to build beyond. *Electrolyte Blood Press* 2024;22:21-28. PUBMED | CROSSREF

34. Jung J, Juarez S, Koh ES, Chung S. Advances in hyperkalemia management and the emerging role of sodium zirconium cyclosilicate. *Electrolyte Blood Press* 2026;24:73-80. PUBMED | CROSSREF

Electrolytes & Blood Pressure (EBP; pISSN 1738-5997, eISSN 2092-9935), the official journal of the Korean Society for Electrolyte and Blood Pressure Research, is a peer-reviewed publication dedicated to advancing research in renal physiology, hypertension, and the cardiovascular system. The journal welcomes original research and reviews addressing glomerular filtration, tubular transport, hormonal regulation, fluid and electrolyte balance, acid-base homeostasis, blood pressure regulation, and toxin elimination. Topics of interest further include the renin-angiotensin-aldosterone system, renovascular and secondary hypertension, and hypertension-related kidney disease—emphasizing the complex interplay between renal function and cardiovascular health. *EBP* accepts contributions from researchers worldwide, across all related disciplines.

1. General Formatting Requirements

1.1. Online Submission

Manuscripts must be submitted electronically via the journal's online submission system at https://www.editorialmanager.com/ebp. Authors may track the progress of their manuscript throughout the peer review process. Revised manuscripts should be submitted through the link provided in the editor's decision letter and should not be submitted as new submissions. By prior arrangement with the editorial office, invited submissions may be emailed directly to: ebp@enbpr.org.

1.2. File Formats

Manuscripts must be double-spaced, include page numbers, and use International System of Units (SI). Acceptable file formats for the main text include Microsoft Word documents (DOC or DOCX). Submissions must include the following:

- Cover letter
- Main manuscript text
- Individual figure files
- Supplementary materials (if applicable, submitted as separate files)

1.3. Language and Style

Authors who are not native speakers of English are strongly encouraged to obtain professional language editing prior to submission. Abbreviations must be defined at first mention in the text, and non-standard abbreviations should be used sparingly.

1.4. Ethical Considerations

All research involving human participants, human data, or human biological materials must have received prior approval from an appropriate institutional review board or ethics committee. Manuscripts must clearly state the name of the approving committee and the approval number. Studies involving animals must also include ethics approval with a reference number. Manuscripts that include identifiable information (e.g., images, pedigrees) must be accompanied by signed informed consent from the subjects involved. Failure to provide adequate ethical documentation may result in immediate rejection.

1.5. Copyright and Permissions

Upon manuscript submission, the corresponding author must sign a license agreement on behalf of all authors, granting the Korean Society for Electrolyte and Blood Pressure Research the rights to publish the work. Authors are responsible for obtaining written permission to reproduce material previously published elsewhere, and such permissions must be submitted at the time of manuscript submission.

2. Manuscript Components

2.1. Cover Letter

The cover letter must include:

1) A statement of the manuscript's significance
2) Disclosure of any conflicts of interest
3) Confirmation that all listed authors have approved the manuscript
4) Confirmation that the manuscript has not been published or submitted elsewhere

2.2. Title Page

The title page should include:

1) Full manuscript title
2) Full names and affiliations of all authors
3) A running title (≤50 characters)
4) Designation and contact details of the corresponding author (mailing address, telephone, fax, and email)

2.3. Abstract

Abstracts for original and review articles must not exceed 250 words. Abbreviations should be minimized, and references should not be included.

1) **Original articles:** Abstracts should be structured under the following headings: Background, Methods, Results, Conclusions.
2) **Case reports:** Abstracts should be structured under: Background, Case Presentation, Conclusions.

2.4. Keywords

Four to six keywords should be listed alphabetically following the abstract. Keywords must be selected from the Medical Subject Headings (MeSH) thesaurus available at https://www.nlm.nih.gov/mesh/meshhome.html.

2.5. Main Text

The main body of the manuscript should be organized according to the type of article submitted:

1) Original Articles:

Reports of original research or novel methodology. Clinical trials must adhere to CONSORT/SPIRIT guidelines. Systematic reviews must comply with relevant reporting standards.

- Structure: Introduction, Methods, Results, Discussion
- Word limit: 4,000 words (excluding references, tables, and figure legends)
- Reference limit: 40

2) Review Articles:

Comprehensive and authoritative reviews, typically solicited but unsolicited submissions will be considered.

- Word limit: 4,000 words
- Reference limit: 50

3) Case Reports:

Reports of rare or novel clinical cases related to renal physiology or blood pressure.

- Structure: Introduction, Case Presentation, Discussion
- Word limit: 1,500 words
- Reference limit: 20

4) Letters to the Editor:

Brief communications, critiques of published articles, or concise case observations.

- Word limit: 800 words
- Reference limit: 8
- No abstract; max 2 figures or tables

5) Editorials:

Commentaries on articles published in the same issue or on broader topics of interest, typically commissioned.

- Word limit: 1,500 words
- Reference limit: 10
- No abstract; max 2 figures or tables

2.6. Acknowledgments

Acknowledgments should follow the main text and may include statements on ethical approval, funding, conflicts of interest, and author contributions.

2.7. References

References should be cited in-text using Arabic numerals in square brackets (e.g., [1]) and listed in order of appearance.

- List up to six authors. If more than six, list the first three followed by "et al."
- Journal titles must be abbreviated according to Index Medicus standards.

Examples:

- **Journal article:** Lee EK, Yang WS. Use of Fludrocortisone for Hyperkalemia in Chronic Kidney Disease Not Yet on Dialysis. *Electrolyte Blood Press* 2024;22:8-15.
- **Supplement:** Kim GH, Han JS. Therapeutic approach to hypokalemia. *Nephron* 2002;92(Suppl 1):28-32.
- **Online publication but not yet in print:** Chao CT, Kovesdy CP, Merchant RA. Sarcopenia, sarcopenic obesity, and frailty in individuals with chronic kidney disease: a comprehensive review. *Kidney Res Clin Pract* 2025 Jan 21 [Epub]. DOI: 10.23876/j.krcp.24.207
- **Entire Book:** Daugirdas JT, Blake PG, Ing TS. Handbook of dialysis. 5th ed. Wolters Kluwer; 2015.
- **Book chapter:** Verbalis JG. Hyponatremia and hypoosmolar disorders. In: Gilbert SJ, Weiner DE, Bomback AS, et al, eds. Primer on kidney disease. 7th ed. Elsevier; 2018. p. 68-76.
- **Website:** National Cancer Information Center. Cancer incidence [Internet]. National Cancer Information Center, c2009 [cited 2009 Oct 20]. Available from: http://www.cancer.go.kr/cms/statics

2.8. Tables and Figures

Tables and figures must be cited in numerical order.

- Table titles should be concise (≤15 words), with legends (≤300 words) placed below each table.
- Figure titles and legends should be provided in the main manuscript file.
- All non-standard abbreviations must be defined.
- Use superscript lowercase letters (e.g., ⋆, †, ‡) for table/figure notes.
- Figures must be submitted as separate files (not embedded), in high-resolution TIFF, EPS, or JPEG (≥300 dpi for color, ≥1200 dpi for line art).

2.9. Supplementary Materials

Supplementary files should be clearly labeled and submitted

separately using the "supplementary" designation. All supplementary materials must be cited in the manuscript (e.g., "Supplementary Figure 1").

2.10. English Editing Certificate

Non-native English speakers must upload a certificate from a professional editing service. Native English speakers should submit a placeholder file labeled "Certificate of English Editing (empty)."

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Manuscripts are acknowledged within one week of submission. Submissions not adhering to technical standards may be returned without review. Each manuscript undergoes blind peer review by at least two external experts. Final publication decisions rest with the Editor-in-Chief.

4. Visual Abstracts (Optional)

Authors of original articles are encouraged to submit a visual abstract summarizing the study graphically. Visual abstracts may be used for online promotion and engagement.

5. Copyright

All accepted manuscripts become the property of the Korean Society for Electrolyte and Blood Pressure Research. A signed copyright transfer agreement must be submitted along with the manuscript.

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7. Post-Acceptance

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7.2 Article Processing Charges (APCs)

- Original/Review Articles, Case Reports: KRW 300,000 (Korea) / USD 300 (international)
- Letters to the Editor: KRW 100,000 (Korea) / USD 100 (international)
- Member Benefit: Fees are waived for corresponding authors who are active members of the Korean Society for Electrolyte and Blood Pressure Research.
- Invited Articles: Publication fees are waived.
- Waivers: Authors from low-income countries may apply for a waiver by contacting the Editorial Office.

The primary objective of peer review is to provide the editorial team with a scientifically informed, balanced, and evidence-based assessment of submitted manuscripts, ensuring that all editorial decisions meet the journal's rigorous standards. In addition, peer review should aid authors in improving their manuscripts, regardless of the final publication decision. Review reports recommending rejection should include a clear explanation of the manuscript's principal weaknesses, thus assisting authors in refining their work for submission to another journal if applicable.

1. General Information

Electrolytes & Blood Pressure (EBP) sincerely appreciates the time, expertise, and thoughtful input contributed by our reviewers. Reviewers play a critical role in maintaining the scientific integrity and academic quality of the journal. When feasible, reviewers are encouraged to assess revised versions of manuscripts they originally reviewed to ensure continuity and coherence in the evaluation process.

2. Confidentiality

2.1. Adherence to Ethical Standards

All peer reviewers must comply with the *Committee on Publication Ethics* (*COPE*) *Ethical Guidelines for Peer Reviewers*. This includes the obligation to:

- Maintain strict confidentiality with respect to manuscript content and peer review correspondence
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Reviewers must not contact authors directly under any circumstances during the peer review process. Any required communication should occur solely through the editorial office.

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Reviewers must not request authorship or suggest that they be added as co-authors at any stage. If a reviewer makes a substantial intellectual contribution that might warrant authorship, they must communicate this to the editorial office via a formal request outlining the exceptional circumstances. Breach of this policy will result in immediate rejection of the manuscript and potential sanctions.

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Reviewers must not involve colleagues, students, or collaborators in the review process without prior written permission from the editorial office. If assistance is obtained with prior approval, the names and affiliations of those who contributed to the review must be disclosed, and proper acknowledgment will be recorded by the journal.

3. Conflicts of Interest

3.1. Identification and Disclosure

Reviewers must assess whether any conflicts of interest exist that could compromise the impartiality of their evaluation. Review invitations should be declined if any of the following apply:

- Recent collaboration with any of the authors (within the last 36 months), including co-authorship or ongoing submissions
- Shared institutional affiliation with one or more authors
- Personal (e.g., family) or professional (e.g., former advisors, mentees) relationships with the authors
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3.2. Obligation to Report

Reviewers must promptly notify the editor or editorial office if any potential conflicts arise after accepting a review assignment. Failure to disclose relevant conflicts of interest may result in sanctions, including removal from the reviewer pool.

3.3. Impartiality and Fairness

Reviewers must remain unbiased and refrain from judgments based on authors' nationality, gender, institutional affiliation, religious or political beliefs, or other personal characteristics. The evaluation should focus solely on scientific merit.

4. Review Reports and Recommendations

4.1. Role of the Reviewer Recommendation

Reviewers are invited to provide a recommendation regarding acceptance, revision, or rejection. The editorial decision will be based on the review reports and the editorial team's judgment, and may not always align with individual reviewer recommendations.

4.2. Focus of the Review

Reviews should prioritize the scientific content of the manuscript

and its alignment with the scope of *EBP*. Minor issues related to formatting and stylistic conventions will be addressed by the editorial office and should not be the focus of the review unless they impede understanding.

4.3. Key Evaluation Criteria

Reviewers are asked to assess manuscripts based on the following:

- Relevance and significance of the topic to the field
- Originality and novelty of the findings
- Rigor and appropriateness of the study design, methodology, and analysis
- Transparency and reproducibility of the data, methodology, and interpretation
- Ethical integrity, including potential issues related to plagiarism, image/data manipulation, redundant publication, authorship disputes, or undisclosed conflicts of interest
- Clarity and quality of the writing, structure, figures, tables, and reference list

4.4. Constructive Feedback

Reviewers should aim to be objective, respectful, and helpful in their feedback. Comments should be specific, actionable, and framed in a professional tone. Authors should be guided toward improving their work, regardless of the final recommendation.

Suggested Review Structure

- General Overview: Provide a brief summary of the manuscript, including its objectives, main findings, and overall relevance. Comment on the significance of the study and its contribution to the field.
- Major Comments: Discuss substantive concerns such as study design flaws, inadequate data interpretation, lack of novelty, methodological weaknesses, or the need for additional experiments.
- Minor Comments: Address less critical issues such as unclear phrasing, inconsistent terminology, typographical or numerical errors, minor referencing concerns, and formatting of tables and figures.

We thank our reviewers for their invaluable service to *Electrolytes & Blood Pressure*. Our reviewers' expertise and commitment to rigorous peer review are essential to upholding the journal's standards and advancing the field.

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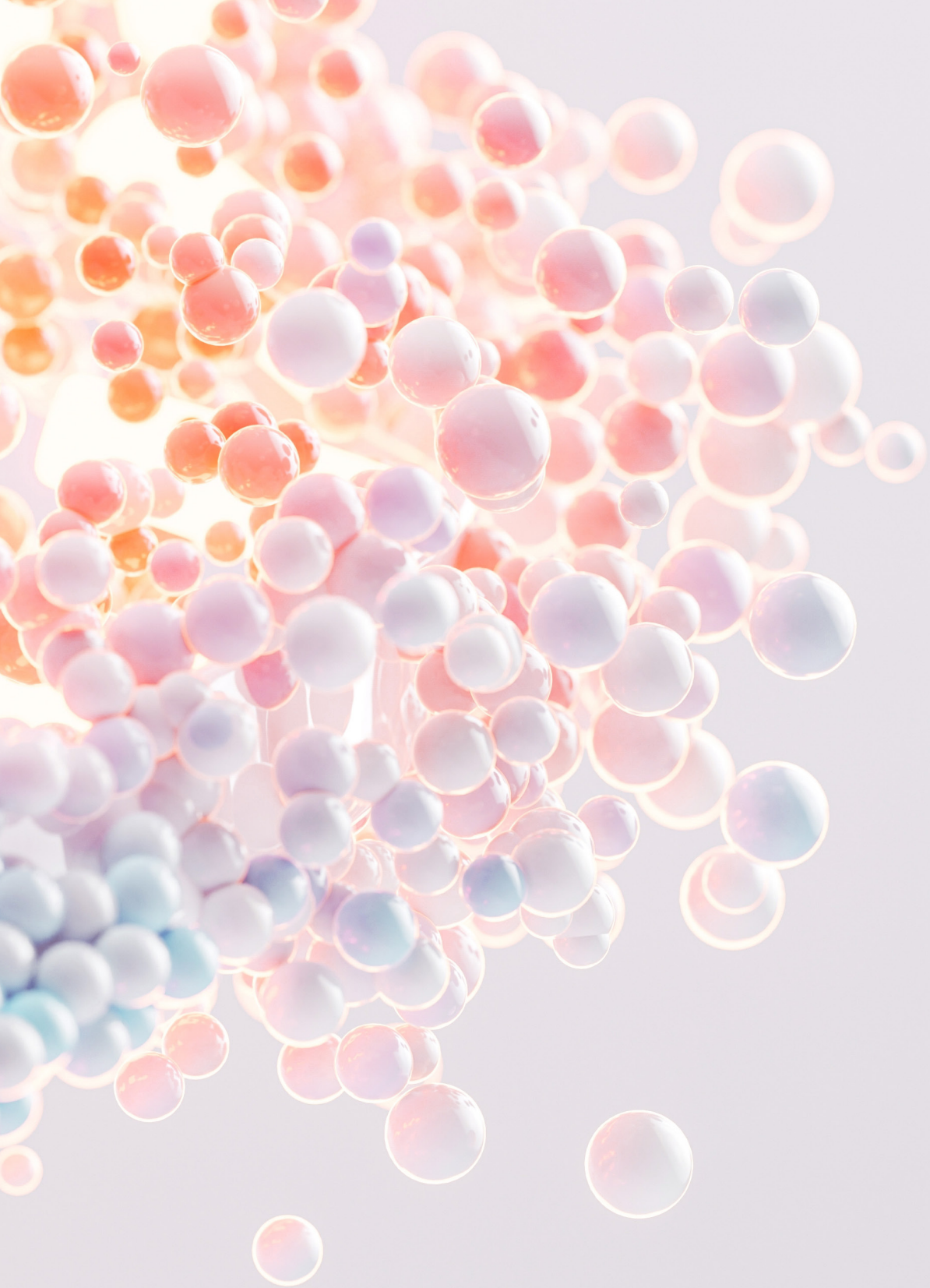

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